



# ENDOCRINOLOGY

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FOR THE STUDY OF

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## MORPHOLOGICAL CHANGES IN THE ENDOCRINE GLANDS IN MONGOLIAN IDIOCY WITH REPORT OF TWO CASES

MURRAY B. GORDON, M.D.

From the Pediatric Service of the United Israel Zion Hospital and the  
Department of Pediatrics, Long Island College Hospital

BROOKLYN, N. Y.

The etiology of mongolian idiocy is as much a mooted point today as it was when the condition was originally described by Langdon-Down (1). The possibility of an endocrine genesis has been the subject of much investigation and discussion, especially with reference to disturbance of the thyroid gland and, to a lesser extent, of the pituitary. This relationship has been suggested on the basis of both clinical association with symptoms referable to dysfunction of the thyroid, numerous examples of which are in the literature (2), and of histo-pathological alteration in these glands as demonstrated on the autopsy table.

The literature on mongolian idiocy as a whole is voluminous but that portion dealing with reports of post-mortem examination of the endocrine glands is comparatively scant. As with most endocrine problems at the present time, the findings have given rise to contradictory interpretations.

Siegert (3) made an intensive study of the literature in 1910 and reported that in the majority of instances normal findings were found on both macroscopical and microscopical examination. He personally feels, however, that in the majority of cases of mongolian idiocy there is at certain times a disturbance of function of the thyroid gland independent of the presence of demonstrable manifestations of hypothyroidism or athyrosis. Kassowitz (4) is also of the opinion that all cases of mongolianism show at times thyroid changes.

Hill (5) reviewed 20 post-mortem examinations of the thyroid gland in mongolian idiocy in the literature and found that morbid changes were noted in several instances as manifested by sclerosis of the gland and degeneration of the colloid substance. He concluded that as yet there is no evidence that any alteration in either the structure or function of the thyroid can be held responsible for this type of idiocy.

According to Wieland (6), the majority of investigators found that the thyroid gland was normal both on microscopic and macroscopic exam-

ination while a small number noted hypoplasia and definite histological changes. The inconstancy of this hypoplastic condition together with the difference in the clinical and anatomical findings in mongolianism and myxedema make him feel that there is no thyrogenetic etiology in this type of idiocy. The occurrence of changes in the thyroid gland and the beneficial results of treatment on isolated symptoms permit the possibility of thyroid alteration in some cases of mongolian idiocy but not in all as claimed by Siegert and Kassowitz.

Thomas and Delhougne (7) observed morphological changes in the thyroid gland of three mongolian idiots. An embryonic type with few follicles and poor colloid content was found in the gland of a  $3\frac{1}{2}$  months infant. The thyroid from a 21-months-old infant showed some areas rich in colloid and others of the embryonal type with poor colloid substance. In the gland of the third infant,  $8\frac{1}{2}$  months of age, the follicles were abundant but were still of undifferentiated tissue and poor in colloid content. The authors consider that these findings may be normal, as the embryonic state may still be present at this age.

Fromm (8) found on post-mortem examination of an 18-months-old mongolian idiot that the thyroid gland showed a development which was insufficient for the age of that child. There was definite hypoplasia and advanced sclerosis as evidenced by an imperfect development of the glandular substance and a deficiency of the colloid substance as compared with an abundant connective tissue.

Brudzinski (9) also reports a thyroid in a rudimentary state in his patient. A partially sclerosed and atrophied thyroid was found by Bernheim-Karrer (10).

Pathological conditions in the thyroid glands of two mongolian idiots were observed by Bourneville (11). "In the first case, the larger and medium vesicles were much more reduced in number, the lobules were less stretched out, the trabeculae were much hypertrophied and the vessels sclerosed. Here and there were interstitial hemorrhages, a little pigment and fatty infiltration. The capsule was uniformly thickened. There were modifications of the thyroid tissue which, though slight, were still pathological. In the second case, the thyroid gland showed alterations in all its elements. In all the vesicles the colloid material was almost completely replaced by cells derived from glandular epithelium. The vesicles were completely choked with these cells. Here and there were numerous vesicles filled with fat. The trabeculae were thickened and infiltrated with young connective tissue. There was extensive sclerosis of the thyroid gland" (Hill's translation) (5). In other cases, Bourneville did not find any abnormal changes.

Phillipe and Oberthur (12) observed slight interstitial proliferation about the capillaries, small hemorrhagic areas and some pigmentation of the connective tissue. Lang (13) reported the presence of colloid degeneration of the thyroid gland with interstitial proliferation in his patient.

In Hill's own cases (5), the thyroid and thymus glands were both apparently normal on gross inspection but sclerosis of the thyroid was found on microscopic examination. This was evidenced by a diminution in the number and size of the vesicles, though they were lined by regular cuboidal epithelium and filled with colloid material which stained well. The interstitial tissue was much increased with much round cell infiltration.

In his text book on Pathology, Kaufman (14) states that he personally never observed any pathological changes in the thyroid gland in mongolian idiocy. Meltzer (15) reports that post-mortem examination of the thyroid glands of four mongolians failed to reveal any pathological findings in any of the glands of internal secretion. Likewise a normal thyroid has been reported by Comby (16), Thiemich (17), Chartier (18), Tilloy (19), Cozzolino (20) and Sutherland (21).

There are very few instances in the literature where complete histological descriptions of the other endocrine glands are given. When mentioned, it is generally stated that they were normal. Hill (5), in his review of 20 cases in the literature, reports that the thymus was always found to be normal. Specific mention of a normal thymus is also made by Comby (16), Thiemich (17), Tilloy (19), Chartier (18), Sutherland (21) and Lang (13).

The only instance of abnormal changes in the suprarenal gland is that reported by Lang (13), who observed what he considered to be necrotic changes. These were evidenced by atrophy of the cell bodies and granular degeneration of the protoplasm; the cells were imperfectly separated from one another and the protoplasm showed diminished receptivity to the stain.

With this inconstancy in the finding of pathological alteration in the endocrine glands in mongolian idiocy, it seems timely to report the histopathological pictures observed in two mongolian idiots. It is of interest to note that not only was the thyroid gland affected in each patient but the other glands were the seat of definite pathological changes.

*Case 1:* M. F., a female infant, 14 months of age, was born at full term by normal delivery and was the only child of young parents who were not related by consanguinity. She presented a typical picture of an associated mongolian idiocy and childhood myxedema as manifested by a small round head, oblique palpebral fissure and superciliary margin with epicanthus, macroglossus, marked hypotonicity of all the muscles, wide open fontanelle, dry skin and hair, cold extremities, incurving of the little finger, large toe separated from the remaining toe by greater distance than normally (prehensile toe). There was a physical and mental delinquency as evidenced by absence of teeth, delay in sitting, inability to walk as yet and no attempt at speech. She has always run a subnormal temperature and had always been constipated. Examination of the eye fundi at the age of seven months revealed normal findings. Roentgenographic examination of the sella turcica at that time showed a small flat type of Class C (Gordon and Bell Classification) (22), within normal limits and shape. The infant had been under my observation at the Endocrine Clinic of the Long Island College Hospital since the age of six months and had been under thyroid and pituitary treatment.

The child was referred by her family physician on Aug. 11, 1928, to the United Israel Zion Hospital with a diagnosis of bronchopneumonia. On admission she presented a typical bronchopneumonia with the usual clinical signs and roentgenographic findings. Blood examination revealed the following picture: Red blood cells, 4,140,000; white blood cells, 7,480; polymorphonuclears, 72; and

lymphocytes, 28. The hemoglobin was 65 per cent (Sahli). The Wassermann and Pirquet tests were negative. She ran a long protracted course characterized by moderate temperature and marked asthenia, finally culminating in death on Sept. 12, 1928.

An autopsy confirmed the diagnosis of bronchopneumonia. On general inspection, all the glands of internal secretion appeared normal with the exception of the thyroid, which was small and firm.

A microscopic study by Dr. Max A. Goldzieher reveals the following changes in the endocrine glands:

*Thyroid:* Broad strands of collagenous fibres separate the thyroid tissue into islands of variable size and shape; some of the islands are invaded by connective tissue. The acini are very small and are lined by a single row of low cuboidal epithelia. Many of the acini are collapsed and appear as solid epithelial structures, while others are slightly distended and appear as small cysts. The colloid content is poor, shows many vacuoles and stains poorly.

*Adrenals:* There is completed involution of the reticularis, the place of the reticularis being taken up by reticular stroma which incloses wide blood filled sinuses. Most of the cortex is formed by well developed trabecularis, whereas the zona glomerulosa is not distinct. The medulla is poorly developed with but a few groups of medullary cells. This is interpreted as physiological involution of the cortex and hypoplasia of chromaffin portion of the adrenal.

*Hypophysis:* This gland is very rich in eosinophile cells and seem well vascularized.

*Ovary:* Shows quite a cellular cortex with a large number of primitive follicles.

*Pineal:* This gland is of fairly large size and encloses a large cyst in its center, the wall of which is formed by glia tissue. The rest of the pineal is quite cellular, most of the cells being large with either oval or round nuclei and with regular distribution of chromatin granules.

In summary, the anatomical findings in the endocrine glands were: Cirrhosis and signs of dysfunction of thyroid gland; physiological involution of adrenal cortex with hypoplasia of chromaffin substance; pineal normal except for the presence of cyst lined by glia cells; normal pituitary gland and ovary.

*Case 2:* Florence K., aged 6 weeks, was admitted to the hospital on Dec. 12, 1927, for a congenital pylorospasm which had produced persistent vomiting from birth and which had resulted in an athrepsia accompanied by dehydration. On admission it was noted that in addition she presented a typical picture of mongolianism with slanting eyes, incurving of the little fingers and prehensile toe. The Wassermann reaction was negative. The blood examination showed white blood cells, 16,170; red blood cells, 4,100,000; hemoglobin, 75 per cent. A differential count, according to the Schilling modification, showed: myelocytes, 2; jungling form, 7; stab kernig, 33; segmented, 28; lymphocytes, 20; monocytes, 10.

The post-mortem findings of interest to the present discussion show a thyroid gland which is small and firm on general inspection and a pituitary which is also small and on section shows peculiar striations.

Microscopic examination of the glands by Dr. Max A. Goldzieher reveals the following:

*Thyroid:* The stroma is considerably increased and bundles of fibres separate the thyroid parenchyma into numerous islands varying in size and shape. Most of the acini are slightly distended and filled with a very thin colloid which stains poorly and is highly vacuolized. The epithelium is of low cuboidal type and forms a single row. Quite a number of the acini are collapsed and appear as solid epithelial structures.

*Adrenals:* The reticularis is in an advanced stage of involution. It is practically substituted by a loose reticulum which encloses blood filled capillaries. There is also iron pigment present denoting previous hemorrhage. The cortex proper shows a fairly large distinct glomerular layer and a markedly developed trabecularis. In the neighborhood of capillaries are seen a few islands of medullary cells.

*Thymus:* The physiological structure of the gland is obscured, as no cortical layer is present. The individual lobules are separated by broad septa of loose connective tissue. Dark lymphocyte-like nuclei permeate the entire lobule irregularly and here and there form larger discrete groups which are separated by much paler medullary cells. The Hassel bodies are very numerous and stand together in groups. The smaller ones consist of concentrically grouped cells of

medullary type while the larger ones show central necrosis, some even appear as small cysts filled with detritus.

**Pineal:** Small, very cellular, and the pineal cells show almost without exception a normal vesicular nucleus. The nuclei of the glia cells are scant.

**Pituitary:** The gland cells of the anterior lobe are rather small, particularly in the periphery. The capillaries between the gland cells are rather wide, sinus-like and lined by conspicuous reticulum fibrils and cells. Occasionally there is a homogeneous faintly staining substance around the capillary separating the latter from gland cells. The gland cells are better maintained in the center of the organ; there the eosinophiles are conspicuous while the basophiles are absent. A small cyst filled with colloid separates the anterior from the posterior lobe. The latter consists of dense nervous tissue with few nuclei.

In summary the findings in the endocrine glands were: Cirrhosis and dysfunction of the thyroid gland; physiological involution of the adrenal cortex and hypoplasia of the chromaffin portion; retrogressive change in Hassel's corpuscles with an increase in number and hypoplasia of the thymus cortex; incipient atrophy of the anterior lobe of the pituitary gland; normal pineal.

### SUMMARY

The histo-pathological changes in the endocrine glands of two mongolian idiots are reported. In the first, 14 months of age, the changes consisted of cirrhosis and dysfunction of the thyroid gland, physiological involution of the adrenal cortex with hypoplasia of the chromaffin substance, a normal pineal except for the presence of a cyst lined by glia cells and normal pituitary and ovary.

The second, 6 weeks of age, presented the following changes: Cirrhosis and dysfunction of the thyroid gland, physiological involution of the adrenal cortex and hypoplasia of the chromaffin portion, retrogressive changes in Hassel's bodies with an increase in number, hypoplasia of thymus cortex, incipient atrophy of the anterior lobe of the pituitary gland and a normal pineal.

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# SEDIMENTATION OF ERYTHROCYTES IN THE ENDOCRINOPATHIES

E. BONILLA AND A. MOYA

Servicio de Patología Médica del Dr. G. Marañón  
From the General Hospital of Madrid

MADRID, SPAIN

In contrast with its use in other diseases the red cell sedimentation test has been but little used in the study of endocrine disorders.

Westergren (1) believes that the thyroid exerts positive influence upon the sedimentation velocity of the erythrocytes. D'Abundo (2) has studied the sedimentation time in dementia praecox patients treated with certain endocrine preparations, and obtained contradictory results. Scuderi (3), using this reaction in different patients, obtained a very rapid sedimentation velocity in a patient with Addison's disease. A very important work is that of Vasaturo (4). He has investigated the sedimentation time in thyroidectomized, parathyroidectomized, thyroparathyroidectomized and castrated dogs and also in clinical hyperthyroidism, hypothyroidism and hypogenitalism. Some of the animals operated upon have been treated with the corresponding endocrine preparations and also the patients with hypothyroidism. From his studies he believes that the hypothyroid patients and the animals without thyroids had a slow sedimentation time accelerated by endocrine therapy. The sedimentation time is also rapid in hyperthyroid subjects. In the parathyroidectomized animals there was observed an augmentation of the velocity and also in a small degree in those animals that were thyroparathyroidectomized. The rate found in castrated dogs and in patients with hypogenitalism showed that the male gonads have no influence upon sedimentation time.

Uyeno (5) found nearly always an accelerated sedimentation time in rabbits fed with thyroid and this seemed to be intensified in accordance with the grade of thyrotoxicosis produced. But he observed a similar acceleration in thyroidectomized rabbits. In simple goiter the sedimentation time is slow, augmenting if the patients are treated with thyroid extract.

Recently, Kafka (6) maintained that while, in the infectious diseases and intoxications, the erythrocyte sedimentation and the viscosity of the plasma agree with each other, in all endocrine diseases the sedimentation time is accelerated and the viscosity diminished.

We have investigated this reaction in different endocrinopathies following the technic of Westergren (7). We use a pipette made by Leitz's house. It was 2.5 mm. calibrated and divided into two hundred millimeters, as far as the highest zero mark which shows the cubic centimeter. The blood is taken from the vein at the elbow with a record syringe. Ex-



amination was made of 2 cc. containing 0.4 cc. of a 3.8 per cent solution of sodium citrate, making the withdrawal without venous compression. The blood was discharged into a tube and then transferred to the special pipette which was supported in a vertical position.

The height of the red cell column was read at the end of one hour, of two hours and in some cases at the twenty-fourth hour. In general we believe that the reaction is definite in the second hour, for we have observed that in certain cases the fall is more rapid in the first hour and then becomes slower. The distances recorded at the end of one hour and of the second hour permits expression of the sedimentation velocity by the following formula:

$$S. V. = \frac{a \div \frac{1}{2}b}{2}$$

in which a represents the first height and b the second.

Since the digestive process hastens the sedimentation time the blood for test is collected before breakfast. Uniquely positive results have been noted in Addison's disease. Last year one of us presented a note, in the "Real Academia de Medicina" (8), on the results obtained in twelve cases and subsequently published a report with the detailed clinical histories and the rate of the erythrocyte sedimentation of twenty-four cases (9). In all these the velocity was rapid, having a special diagnostic interest in its constant acceleration in very atypical clinical cases.

The importance of studying the erythrocyte sedimentation in Addison's disease is seen if one takes into consideration the fact that in the clinic Addison's disease is difficult to diagnose, as one of us has persistently repeated (10), (11), and that the other laboratory data (hypoglycemia, hypocholesteremia, etc.) are very inconstant. The blood sugar curve after a glucose meal at times is of the high type though the initial level may be low, as has been noted in some of our cases.

As is well known, in the subjects with hypoadrenalism several causes (infections, intoxications, traumas, surgical intervention, insulin injections or vaccines) are able to cause severe accidents, even sudden death. From this one deduces, as we said in a recent conference (12), the great desirability of early recognition of adrenal deficiency in all patients, whether these are to undergo operative or the medical treatment already mentioned. This permits one to take all necessary precautions for avoiding mishaps and to avoid the employment of medicaments that may be contraindicated. Marañón (12) recommends in these cases the systematic study of the blood sugar and we believe that it would be useful to determine systematically the sedimentation velocity.

From the study of our cases we believe that the more grave is the adrenal involvement the more rapid is the sedimentation velocity. The velocity test, therefore, has considerable prognostic value and permits us

to balance to a certain degree this laboratory datum with the clinical data of the account of the arterial tension.

In this manner we see that in secondary Addison's disease (14), always less grave, the arterial tension is maintained for some time at the characteristic levels of primary adrenal insufficiency, and the erythrocyte sedimentation takes place also less rapidly. In these secondary cases the principal lesion occurs in the cortex and this makes one think that the acceleration of the sedimentation velocity is principally due to disturbances of the medulla.

We do not know the mechanism for producing this phenomena in the patients with Addison's disease. Our first thought is that it is due to a tubercular condition which is the underlying cause of the disorder in a great many of the Addison's disease cases. But in two of our own cases it was proved at autopsy that the adrenals were invaded by a sclerotic process without active focus in the chromaffin tissue nor in any other part of the organism. We could not discover them either by clinical observation or radioscopy in the other patients.

More recently Morros Sardá and one of us (15) has studied the blood chemistry in two epileptics before and after the extirpation of one adrenal gland, an operation which, as is well known, has been recommended principally by Fisher to combat the convulsions. The sedimentation velocity which before operation was three and two millimeters, respectively, had increased, after twenty-five days, to 46.2 and 59. This observation is of great interest as bearing out the diagnostic value of our sign and showing that it bears a direct relationship with the adrenal incretion without any necessary relationship to the tubercular process as such.

Pico, Franceschi and Negrete (16) have studied in horses the influence of insulin upon erythrocyte sedimentation without obtaining any positive results. But they have noted that in these animals in which the blood sugar was low before the injection of insulin, the sedimentation velocity was always accelerated. In many of our Addisonians the rapid sedimentation coincided with a normal or somewhat elevated blood sugar level, and in other patients with other and different diseases tested in this respect no relationship between the two data could be detected.

In some of these simultaneous investigations of the sedimentation velocity and the blood sugar level before and half an hour after the injection of 30 units of insulin it was found that variations in the sugar level had no influence on the sedimentation velocity.

Recently, Nitzescu and Missir (17) have studied sedimentation velocity in dogs before and after extirpation of the whole pancreas and have noted that it is more rapid after the operation, more or less in accordance with the degree of gravity of the diabetes thus produced. From all these observations it seems evident that the hypoglycemia in Addison's disease is not the factor which leads to acceleration of the sedimentation velocity.

According to Kürten (18), the relation of leechemia and cholestere-mia plays an important part in the erythrocyte sedimentation, since on this relation depends the ionic permeability of the cellular membrane, the water content of the plasma and the electric capacity and resistance of the erythrocytes; he believes that the sedimentation velocity is the more rapid the greater the cholesterol content of the blood. This conception is not in accordance with the investigations of Salomon, De Potter and Valtis (19) nor our own observations because in many of our patients with Addison's disease the blood cholesterol level was low.

The results obtained in other endocrinopathies are set forth in the following table.

Name	Diagnosis	Basal Metabolism	Sedimentation Velocity
J. B.	Hyperthyroidism	+50	6.75
E. J.	Hyperthyroidism (reactional to pyelitis)	+30	5.00
M. M.	Hyperthyroidism	+60	19.00
E. L.	Hyperthyroidism	+45	18.00
J. S.	Hyperthyroidism	+28	6.00
S. V.	Hyperthyroidism	+67	4.5
M. L.	Hyperthyroidism	+40	2.40
F. S.	Hyperthyroidism	+82	21.50
N. H.	Juvenile goiter with light thyroid reaction	+12	9.00
A. P.	Hyperthyroidism	+32	10.25
M. F.	Hyperthyroidism	+18	6.00
C. S.	Hyperthyroidism	+51	13.75
A. R.	Hyperthyroidism	+39	12.70
B. A.	Goiter with hyperthyroid reaction	+15	2.15
M. N.	Myxedema	-45	15.9
T. E.	Myxedematous infantilism	-30	9.5
L. S.	Myxedema	-50	91.5
M. D.	Acromegaly	....	14.20
A. L.	Acromegaly	....	37.00
V. P.	Hypophyseal tumor, Froehlich's Syndrome	....	3.10
J. S.	Hypophyseal tumor, Froehlich's Syndrome	....	44.00
F. C.	Hypophyseal tumor with genital atrophy. Geroderma syndrome without adiposity	....	3.00
M. B.	Diabetes insipidus	....	12.50
A. S.	Diabetes insipidus	....	17.50
Z. P.	Hypophyseal dwarfism	....	21.00
F. P.	Geroderma	....	20.37
	After graft	....	26.50
A. D.	Puberal intersexuality of adipose type	-18	3.87
V. Z.	Eunuchoidism	....	28.25
A. B.	Macrogonitosomia	....	16.00
J. U.	Ovarian insufficiency	....	42.00
Y. V.	Ovarian insufficiency	....	57.50
R. P.	Ovarian insufficiency	....	3.00
H. O.	Ovarian insufficiency	....	23.00
M. V.	Ovarian insufficiency	....	12.50
A. L.	Ovarian insufficiency	....	4.20

From the perusal of this table it is seen that in 14 cases of hyperthyroidism the rates were rather slow, but otherwise normal (a finding which is contrary to that of Vasaturo and Uyeno) without regard to the intensity of the clinical manifestations nor of the existing basal metabolic rate. Of three myxedematous subjects two had normal and one had an extraordinarily accelerated velocity. In our hypophyseal cases we found the sedimentation velocity normal in one acromegalic and somewhat rapid in another. Of the three cases of hypophyseal tumor with hypofunctional symptoms a slower velocity was found in two and a more rapid in one. In two cases of diabetes insipidus the velocity was normal. In one case of dwarfism the rate was somewhat rapid. In the cases of genital dis-

turbance (gerodermia, eunuchoidism, intersexuality, macrogenitosomia) the velocity findings are completely contradictory. It is worthy of note in the case of gerodermia in which we investigated the sedimentation velocity before and after graft of testicular substance, according to the procedure of Voronoff, the procedure made no difference.

From our investigations we deduce consequently that the thyroid, hypophysis and the genital glands have no important influence on the sedimentation velocity and, with the exception of Addison's disease, the sedimentation velocity is without diagnostic value in the endocrinopathies.

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# THE EFFECT OF CASTRATION ON THE PROLIFERATIVE ACTIVITY AND STRUCTURE OF THE THYROID GLAND IN GUINEA PIGS

K. S. CHOUKE, M.A., M.D.

From the Department of Pathology, Washington University  
ST. LOUIS

and the Department of Anatomy, University of Colorado  
DENVER

The object of this investigation is to determine if extirpation of the ovaries has any definite effect on the structure and especially on the proliferative activity of the thyroid gland. For this purpose the thyroid gland of the guinea pig was used, for it has been studied previously in a series of investigations by Loeb (1) and his associates, Gray (2), Rabinovitch (3), and McCordock (4). These authors used two methods for determining the effect of various factors on the thyroid gland. In the first place, Loeb (5), in experiments begun in 1919, used the intensity of compensatory hypertrophy which follows extirpation of three-fourths or more of this organ, as a convenient indicator of the activity of the gland. In the second place, Loeb, Gray, McCordock and Rabinovitch made use of the normal gland and here attempted a quantitative measurement of the effect of various factors on the thyroid gland by studying in a quantitative manner the number of mitoses in the acini together with the changes in the size of the acini, of the acinus cells, of the consistency of the colloid and of the number of phagocytes.

The first one of these two methods, namely, the determination of the degree of compensatory hypertrophy, was also employed more recently by Furuya (6), who used, however, the rat for his experiments in which he determined the influence of castration on the intensity of compensatory hypertrophy. This author found that in four female rats which had been castrated compensatory hypertrophy was more pronounced than in two non-castrated female rats. Furuya did not make a microscopical study of the gland but he merely compared the weights of the remaining lobes after extirpation of one lobe of the thyroid gland. Furthermore, he did not compare the structural differences in the normal and castrated animals. It is evident that the relatively slight differences in weight found under those conditions might be greatly influenced by secondary conditions as, for instance, the amount of blood retained in the gland or the amount of adherent fat tissue or the quantity of colloid within the acini. There is also the probability that the two lobes of the gland are not in every case equal in weight.

In our experiments we used the guinea pig, the behavior of whose thyroid was well known through the previous studies mentioned above.

Both ovaries were removed in fourteen animals under ether anesthesia. At varying periods from 14 to 323 days after the operation the animals were killed with chloroform, the thyroids removed immediately and fixed in Zenker's fluid. One or both lobes of the thyroid gland in each case were cut serially. Nine animals were used as controls. Their thyroids were likewise cut into serial sections, either one lobe or both lobes being used in the various experiments. The two groups of animals were kept under as nearly identical conditions as possible. The control animals were killed at the same time as the castrated animals and the thyroid glands were fixed and stained by the same methods.

The proliferative activity in each gland was determined by counting the mitoses in every tenth section in accordance with the previous work from this laboratory. In addition, in studying the sections, the size of the acini, the character of the acinus cells and the condition of the colloid and, in particular, also that of the phagocytic cells in the colloid were compared. The results were as follows:

The average number of mitoses in 14 castrated animals was 245 per gland. But if we exclude in this series the count in guinea pig 393, which seems, for some unknown reason, to be exceptionally high, then the average count is only 186 mitoses per gland including two lobes but omitting the isthmus. A summary of the mitotic counts and of the changes in weight which may influence the mitotic activity in the castrated animals is given in Table I.

TABLE I  
CASTRATED GUINEA PIGS

No. of Guinea Pig	No. Days Between Castration and Removal of Thyroid	Mitoses*	Original Weight in Grams	Final Weight in Grams	Gain or Loss of Weight in Grams
314A	14	156	315	380	+65
317	14	49	525	503	-22
390	22	246	423	460	+37
315A	28	414	300	365	+65
920	28	254	485	510	+25
13	42	51	550	525	-25
14	42	51	575	563	-12
392	43	226	?	?	?
744	49	182	500	?	?
393	56	1024	320	420	+100
316A	61	122	330	535	+205
919	69	96	345	480	+135
317A	90	182	355	675	+320
1000	323	384	?	925	?
Average	63	245	418	528	+81

\*Mitoses, per whole gland, excluding isthmus.

None of these animals was in heat.

In the control animals the average number of mitoses was 203 per gland. It is unnecessary to give here a description of the normal guinea pig thyroid because it corresponds very closely to that given by McCordock (4). The average number of mitoses per gland in the castrated animals does not deviate very widely from that of the controls. As a matter of fact they can be considered of the same order and within the range of the experimental error.

Evidently there is an increase in the number of mitoses which runs parallel with the increase in the weight of the animal during the period of the experiments, and which is also found in the case of the controls. This confirms the previous observations of Loeb (1) and Rabinovitch (3).

The weight of the castrated animals varied between 300 grams and 925 grams; the average weight was about 470 grams. If we exclude the one older animal weighing 925 grams, then the average weight of the group would be about 455 grams.

The weight of the control animals ranged between 165 and 555 grams; the average weight for this group was about 400 grams. The weights and number of mitoses per gland for the control animals will be found in Table II.

TABLE II  
CONTROL GUINEA PIGS

No. of Guinea Pig	Mitoses	Original Weight in Grams	Final Weight in Grams	Gain or Loss of Weight in Grams	In Heat or Not
x	122	?	?	?	No
11	40	500	440	-60	No
12	30	550	555	+5	No
240A	546	255	314	+59	Yes
327A	362	315	525	+210	Yes
231A	140	225	230	+5	No
329A	528	165	275	+110	Yes
97	38	?	480	?	No
920A	22	?	495	?	No
Average	203	335	414	+55	....

In this table an interesting feature is noticeable, namely, that the animals which were in heat at the time of removal and fixation of the thyroid gland for microscopical examination show a much larger number of mitoses in the total gland than the animals that were not in heat at the time of examination. However, at present we consider this finding merely as suggestive and it is intended to confirm this observation in additional experiments.

Again it is noticeable that the decrease in the weight of the animal coincides with the decrease in the proliferative activity of the gland.

## DISCUSSION

There does not seem to be any definite relationship between the number of mitoses and the number of days which elapse between the time of castration and the removal of the thyroid gland for purposes of examination. There occurred, however, a few exceptional cases. Guinea pig 393 shows 1024 mitoses for the whole gland; this number seems to be unusually large for the series. No explanation appears to be available for this finding.

Guinea pig No. 1000, examined 323 days after castration, needs especial mention in this series. In this animal the acini were larger than in any other guinea pig of the series. The colloid was hard and considerably retracted from the walls of the acini. The epithelial cells of the acini were flattened in this gland. This flattening was apparently due to pressure exerted from within the acinus cavity by the colloid. There were scarcely any phagocytes noticeable. We are justified in assuming that these changes were caused by the advancing age of the animal because several other older guinea pigs examined especially from this point of view showed a similar structure of the thyroid gland. For the most part, there is no marked difference in the size and character of the epithelium and of the acini between the control and castrated female guinea pigs, although noticeable variations are present in individual cases even in the control animals as mentioned by Gray and Loch (2).

Furuya (6) experimenting with rats and dogs removed one-half of the thyroid gland and weighed it. In four female rats he removed the ovaries at the same time, and kept the other two as controls. He castrated one female pup and kept the other one as a control. Thirty-two days after the operation he killed these animals and weighed the remaining piece of the thyroid gland. He found that this remaining half of the gland had increased in weight in the castrated female rats 30 to 50 per cent more than in the controls.

This difference may be caused by a number of factors, as stated in the early part of this paper.

Several years ago, Dr. Julius Elson carried out some experiments in this laboratory in which he tested the effect of castration on compensatory hypertrophy of the thyroid gland in guinea pigs. His work is not complete and remains unpublished, but as far as it went there was no definite effect of castration noticeable on the hypertrophic changes found in the thyroid gland.

## SUMMARY

Castration in female guinea pigs causes neither any appreciable change in the proliferative activity nor in the structural characteristics of the thyroid gland.



The structure of the thyroid gland of the guinea pig seems to show a tendency toward an increase in the amount of colloid and toward a flattening of the acinar epithelium with advancing age.

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# THE OCCURRENCE OF YEASTS IN PATIENTS WITH THYROID DISEASE

J. ARTHUR BUCHANAN, M.D., M.S. in Med.

BROOKLYN, N. Y.

The types of thyroid disease indicated by the title of this paper are exophthalmic goiter, colloid goiter, adenomata, and myxedema.

For four and one-half years I have been investigating patients with lesions of the skin due to fungi. As there is no known method of permanently curing the condition, it seemed obvious that there must be some continued source of contamination. The gastric contents and stools were cultured to ascertain if the intestinal tract was the focus of continual contamination. These cultures were positive on either the first or second trial in every instance. The gastric contents yielded more abundant cultures in many instances than the stools. As many of the patients had annoying sensations in the mouth, the saliva was cultured. The saliva was positive for yeasts in all instances where the cutaneous condition was at all marked. When the saliva was negative, the gastric contents or stools, or both, were positive. The saliva cultures offer a ready method of investigation. The organisms in many instances were grown in various types of sugar solutions. All of the organisms produced alcohol from the fermentable sugars.

The next step in such a study is to determine if the organisms produce the same types of poisons in the body of the patient as in the test tube. The urine of the patients was tested for alcohol and other products of yeast metabolism by the bichromate and iodoform methods (1). The tests were positive in every patient. The degree of positiveness has no relationship to the specific gravity, nor to the acidity of the urine. The acidity of the urine is, however, directly related to fermentative activities in the intestine. These tests are not positive in the urine of patients if fermentation by yeast is not taking place. The use of the tests makes it unnecessary, except for statistical purposes, to culture the various sections of the gastro-intestinal tract.

The bichromate and iodoform tests are utilized for the group of alcohols resulting from yeast metabolism (2). Besides alcohols, aldehydes, and other undetermined substances are formed, which cause reduction. There are many acids formed, which are apparently non-reducing to bichromate. The most common type of alcohol produced is ethyl. The odor of acetaldehyde in the bichromate test shows that ethyl alcohol is excreted unoxidized in the urine, and is oxidized in the test. In some instances there is no odor of acetaldehydes. The quantities of amyl, propyl, and butyl alcohols produced by yeasts are much less than that of ethyl. The amount of any type in the body depends on the diet, and the particular

type of organism present. Attempts to isolate the different types of alcohol in the urine offer some possibility of securing helpful information, but the quantities that might be present are so small that the task would require much effort. The practical application of the search is not important, as the dietary changes cause considerable variation from meal to meal. The metabolic faeultics of a particular yeast from a patient are better determined in an incubator by the use of various types of solutions and solid media.

#### EXOPHTHALMIC GOITER

Mr. I. S., 39 years of age. Seven months before the patient came for examination, he became very restless, and lost weight rapidly. The heart was rapid, and he felt weak in the thigh muscles. For several months the eyes had been prominent. The patient had always enjoyed good health except for bloating after meals and, at times, pain in the epigastrium. The bowels had always been constipated. He had suffered in the last few months from frontal and occipital headaches. The basal metabolic rate was +79. The urine gave a high test for alcohol and other products of yeast metabolism. The saliva cultures showed every inoculation of the media positive for yeasts. The patient was placed on a special type of diet, which has been developed for the treatment of cutaneous lesions due to fungi, (3) and given Lugol's solution three times each day. At the end of six weeks he had gained twelve pounds. The pulse rate was normal, and the basal metabolic rate was +12. At the end of six months he had gained nineteen pounds. The pulse and metabolic rates were normal. He felt well in every way.

The urine observations have been repeated on two other patients. They were patients of surgeons, and have been treated surgically. The end result in one is not satisfactory, and the other has not been traced.

#### COLLOID GOITER

Mr. P. H., aged six years. This patient has been under my continuous observation since he was two years of age. He came originally because of a cutaneous condition, which was considered to be eczema. He also had asthma. He suffered from the formation of gas in the intestine, and the mushy stools were usually pale in color. They were very acid in reaction, and contained much gas, but nothing characteristic was found. He had various types of skin tests for foods, and in spite of changing the diet to comply with the indications of the tests, he had no improvement in any of his symptoms. When he was four years of age a small goiter became noticeable. It was smooth and soft. When he was four and one-half years of age his skin began to be coarse, the hair dry, the lips thick, and the eyelids puffy. He was less alert mentally. A basal metabolic rate was -25. He was put on small doses of thyroxin, and the physical evidences of thyroid deficiency disappeared. The metabolic rate became normal. As the myxedematous condition developed the thyroid gland decreased in size. The skin condition showed no change during this period. The saliva was not studied for yeast organisms until February, 1929. It was positive. The urine gave a high reading by the bichromate and iodoform tests.

Four other patients with colloid goiter have been studied. One had ringworm of the chest about five months before the goiter appeared. They all showed the same urine findings, and in the one instance where the saliva was cultured it was positive.

#### ADENOMATA OF THE THYROID GLAND

Mrs. A. M., aged 63 years. Eleven months before the patient was first seen she noticed that a lump was forming in the midline of the neck. It was firm, and seemed to be increasing slightly in size. For a slightly longer time she had noticed itching over the back of the neck, and in the antecubital spaces. She had suffered for years with a great deal of gas on the bowels, and constipation. In her earlier life she had suffered from attacks of headache, associated with nausea and vomiting. The attacks ceased one year before the onset of the skin and thyroid trouble. There was a small firm tumor in the midline of the neck in the isthmus of the thyroid gland. There were no evidences of

hyperthyroidism. Over the antecubital spaces there were many small papules with fine points, which contained a small quantity of clear liquid. The same condition was on the back of the neck. The saliva was positive for yeasts, and the urine gave a high reading by the bichromate and iodoform tests. The patient was put on the special diet, and in a short period of time the skin had cleared up entirely. The thyroid nodule shows no decrease in size, but is becoming less firm in consistency.

The studies on the urine have been repeated with similar findings in three other cases. It is difficult to find a considerable number of patients with this condition who do not have other diseases.

#### MYXEDEMA

In two cases, besides the boy reported above, the urine has been examined. It was positive in both instances. In these two cases there were marked cutaneous lesions due to fungi. Both patients had had years of gastro-intestinal trouble characterized by gas formation, and constipation before the onset of the myxedema.

#### RELATIONSHIP OF YEASTS TO DISEASE

The presence of yeasts in the intestinal tract has been known for a considerable number of years. The relationship to pathologic conditions has been questionable. There seems to have been no one who thought of yeasts in the intestine in terms of alcoholic fermentation. The possibility of alcoholic fermentation taking place in the intestine makes their relationship to various pathologic conditions of man very reasonable. In plants their pathogenicity is associated with this process (4). The relation of alcohols to various types of physical conditions, as well as symptoms, is well known. The manufacture of it in the body must necessarily be associated with marked changes and disturbances. Ethyl and propyl alcohol both boil at less than body temperature, so that their presence in even minute amounts would cause unpleasant sensations in the intestine. One of the usual accompaniments of this type of fermentation is the production of gas. There are some yeasts which do not produce gas. They act as oxidizing agents. Yeasts form some of the highest types of alcohols known, and the physical changes in the body associated with an organism of this type would be much more frank than those associated with the organisms producing the lower types of alcohol. The aldehydes produced by yeasts are powerful reducing agents (5). The end products of yeast metabolism vary with the type of media, and with various concentrations of the media. In man this would apply to the inherent chemical constitution of the individual, as well as to the type of food consumed. An organism might cause in two individuals two different conditions, because all individuals, if they could be analyzed to their chemical finality, would be slightly different.

At present there is no simple, or even complex, accepted method of definitely determining the classifications of yeasts. All of the yeasts studied from goiter patients ferment glucose. They grow in sugar solutions as bottom yeasts. The colonies are white in color on Sabouraud's media, and on beer wort agar. As there is such considerable variation in the physical condition of the cells and of their biologic characteristics with

age and nutritional conditions, it seems better to await future developments before attempting to list specifically many of the yeasts found in patients.

The significance of yeasts in patients is most quickly determined by treating patients with cutaneous lesions caused thereby by dietetic methods. The laboratory and the clinical changes in this group of patients furnishes the criteria for considering similar data in patients without cutaneous lesions as indicative that the pathologic expressions in the latter group are the results of yeast metabolism.

All metabolic processes of yeasts are associated with the formation of enzymes and co-enzymes, which are oxidative and reductive (6). The absorption of these foreign enzymes into the blood stream furnishes the mechanism for a disturbance in these basic reactions in the body. This absorption shows that they could be passed through the placenta of the mother to the child, or even through the milk.

#### BASIC CHEMICAL DISTURBANCE CAUSED BY GOITER

When a goiter is affecting the body in a somatic way, it expresses itself as a disturbance of oxidation. Iodine when in its proper combination in thyroxin, which is the known important secretion of the thyroid gland, is responsible for about thirty-five per cent of the rate of oxidation processes in the body. The formation of excess amounts of thyroxin, as in adenomata, leads to excessive oxidation. The presumably altered type of secretion that is formed in exophthalmic goiter leads to excessive oxidation, but there are some physical changes produced in the body that do not accompany the events associated with the increased oxidation due to adenomata. In myxedema there is loss of gland tissue, so that there is a decrease of oxidative processes. In colloid goiter there is some alteration in the functional activity of the thyroid cells so that they secrete more colloid material than in the normal. The activity of the cells is apparently less than in the normal, but not sufficiently less to decrease materially oxidative processes generally in the body. There is no reason to believe that the formation of a tumor in the thyroid gland has a cause different from that of tumors elsewhere. Whenever a tumor partakes in the functional activities of the gland in which it is located, it follows the same line of functioning as is typical of the structure in which located.

In studying conditions due to yeasts, it must be borne in mind that their activity depends on enzymes and co-enzymes. All cells come from cells. Enzymes come from enzymes. Like produces like. All enzymatic action is reversible. Two enzymes of like type lead to acceleration of activity, and the reverse. Hypertrophies and atrophies result from such activities, as is well shown in many fungal diseases in plants, vegetables, and trees. The study of such diseases has great comparative value (7), (8), (9).

## THE STOMACH INTESTINE AND THE SITE OF GOITER PRODUCTION

The painstaking investigations of McCarrison established definitely that the causal factor of simple goiter is, in some cases, at least, in the intestinal tract (10). The marked gastro-intestinal symptoms of patients with exophthalmic goiter furnish criteria to show that there is some type of irritation in the intestine of such patients. McCarrison showed that goiter could be readily transmitted by fecal contamination. He described spores in the stools of patients, and evidently felt that they came from bacteria. He made no cultures for yeasts. He demonstrated that something associated with food, water, soil, and fecal matter was fundamentally causative of goiter. McCarrison did not consider iodine deficiency to be primarily causative, although he had evidence to show that iodine was in some way important. In the treatment of patients, he obtained equally as good results with the use of thymol, salol, and B-naphthol, as with iodine.

## RELATIONSHIP OF IODINE TO GOITER

The place of iodine in goiter therapy and prevention has been well established. The reason has not been determined. Its action is most marked in colloid goiter and exophthalmic goiter. There is still some debate about its use in the treatment of hyperthyroidism due to adenomata, and some suspicion that it will cause adenomatous goiters to become hyperactive. The evidence when finally sifted seems to indicate that it is just as valuable in the treatment of this type of hyperthyroidism as that of exophthalmic goiter, and that it does not lead to hyperactivity of the adenomatous goiter.

The soil of most countries that have long been inhabited have been fertilized by animal and human excrement. In animal excrement yeasts, and other types of fungi, are abundant. In human excrement the same state prevails. McCarrison by careful experiments showed that such filthy habits of fertilizing the soil by groups of people rendered the soil more productive of goiter, because the causal factor in such soils is greater than the quantity of iodine. Pasteur found yeasts, as well as other types of fungi, in the soil at all four seasons of the year. The viability of yeasts is something that receives little consideration. Guilliermond has studied this problem (11). The older the civilization, the greater the prevalence of fungus-caused diseases should be, because of certain customs associated with soil fertilization. The sewage is disposed of into the streams and rivers. Water drains from the soil into the same streams and rivers. The water is studied as to bacterial content, but not as to the presence of yeasts and yeast products. The enzymes and co-enzymes of yeasts are also in the water, so that water may be harmful even after the yeasts are removed by filtration.

Fruit and vegetables are grown on polluted soil, and are thereby contaminated. The careful analysis of the symptoms of patients with yeast-

caused lesions of the skin indicates that eating vegetables that are grown in excrement fertilized soil lead to gastro-intestinal disturbances, essentially as gas production. White potatoes, carrots, cabbage, and turnips have been most frequently associated with development of the untoward signs. Among fruits, strawberries and cantaloupes are the most common offenders. The highly active ferments of lima and kidney beans belong in a different category. Their tendency to form gas in the intestine can be largely controlled by adding a few drops of iodine to the water in which they are cooked or by having the individual take five or six drops of Lugol's solution in milk during the meal.

McCarrison demonstrated that iodine rich soil was antagonistic to the state of the ground, which led to goiter production. The quantity of iodine required to be antagonistic to the septic state of the ground which may result from long periods of fecal contamination is infinitely less than required to prevent yeast multiplication and activity in the test tube or in man. The nutritional status of the soil everywhere and the annual temperature ranges in some localities are of themselves marked deterrents to yeast multiplication. Similar data were collected in water in relation to iodine and goiter production, and showed that the iodine was effective in relation to fecal contamination. After analyzing Marine's work in connection with hyperplastic goiter in artificially reared fish, McCarrison concludes that the iodine relationship is one of insufficiency relative to the living conditions of the fish. Liver and liver extract lead to rapid multiplication of microscopic fungi. The water in the lower tanks becomes increasingly more contaminated by fecal discharges of the fishes in the upper tanks. The same principle applies to man in relation to soil, food, and water.

Iodine rich soil contains 400 parts of iodine to ten million parts of soil. On this type of soil animals confined in dirty cages did not develop goiter. Iodine rich drinking water contains 300 parts of iodine in 100 billion parts of water. The quantity of iodine required in the presence of one-tenth of a Fleischmann's yeast cake in order to inhibit fermentation and multiplication ranges from 36 to 360 parts in 75,000 parts of water.

If yeasts cause goiter, and iodine has a definite place in both its treatment and prevention, iodine must have a basic relationship to the life of yeasts. The question may be settled in a striking fashion. Put a yeast cake into a liter flask that is nearly filled with water containing a quantity of sugar, and incubate the mixture at 37.5° C. until fermentation is active, as shown by the rapidly rising bubbles. At this time add Lugol's solution drop by drop. The fermentative activity becomes less and less until it finally ceases. The reaction is quantitative, and relative to the activity of the yeasts. The variability in the activities of yeasts must not be overlooked. If a series of ten fermentation tubes is arranged, all containing the same quantity of a very active yeast, and sugar in twenty-five cubic

centimeters of water, to which Lugol's solution is added by drops according to the number of the tube, the amount of gas rising into the gas tube will be as a descending staircase from tube one to tube ten. In less active yeasts there may be only fermentation in the first three tubes. In all specimens the fermentation has been active in tube one. The same quantity of yeasts was used each time. The concentration of iodine is 36 to 360 parts to 75,000 parts of water. Exact quantitative measurements of gas produced have no value, because of the difference in activity of different specimens of yeast. All of the other intestinal antiseptics used by McCarrison have a similar action on yeast fermentation. Temperature ranges beyond a certain limit have a similar action. There is no multiplication of the yeasts in the tubes containing enough Lugol's solution to stop fermentation entirely. The quantity of iodine required in man to stop gas production by yeasts in the stomach has been found to be quite variable.

The value of iodine in the soil, and in the treatment and prevention of certain diseases, which are the expression of yeast action in the intestine, is clear. Iodine, in sufficient dosage, is a depressant to cellular activity and multiplication, so that its action is two-fold in the goiterous individual. Iodine in minimal amounts is a stimulant to cellular activity and multiplication. The present investigation may be completed by a cultural study of yeasts in the soil of goiter areas in relation to the iodine content of the soil. I am not in a position to make this investigation.

#### THE SUCCESS OF LUGOL, THE PHYSICIAN

When studying the life of this physician, I was quite unable to determine why he was so successful (12). He called all of the diseases that he treated scrofula. He treated them all by various combinations of iodine. The reasons for his success become obvious when one is familiar with the great prevalence of yeasts in nature.

#### SUMMARY

All types of thyroid disease are associated with fermentation by yeasts. Yeasts may be found in all patients when proper cultures are made. The results of iodine and other types of therapy, that are inhibitive in alcoholic fermentation, indicate their presence to be causal factors of the disease with which their presence can be demonstrated. Iodine in proper amounts prevents the excessive multiplication of yeasts in the soil, and thereby lessens food contamination. The presence of large amounts of iodine in food and water would be preventive of goiter in man, and also of myxedema. Present methods of treating thyroid disease are empirical.

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# DISTRIBUTION AND PREPARATION OF THE OVARIAN FOLLICULAR HORMONE

J. A. MORRELL, E. W. McHENRY AND H. H. POWERS

From the Biological Laboratories, E. R. Squibb & Sons

NEW BRUNSWICK, N. J.

Investigators have shown that the follicular or estrus-inducing hormone occurs in the various component parts of the ovary, in the placenta, and in the circulating and menstrual blood of women. Because of the relatively low yield obtainable from ovaries and the scarcity and high cost of these glands a systematic search was instituted to locate if possible a rich source of the hormone. This was essential in order to place any preparation in the hands of the clinician for use in treatment of the ovarian hypofunctions.

## EXPERIMENTAL PROCEDURES

The general method outlined by Allen and Doisy, which consists of a modification of that described by Iscovesco, was employed in obtaining the extracts from the different materials used. These preparations were oil-soluble and were tested in olive oil solution according to the technique described by Allen and Doisy. That is, three injections were administered to spayed rats at 4 hour intervals and vaginal smears taken 36 and 48 hours afterwards. Five rats were placed on each dosage and four out of five must show full cornified spreads for a unit.

A typical example of the procedure followed is given. Fifteen lbs. of sow kidneys were ground and extracted with agitation for four hours

TABLE I

YIELD IN ALLEN-DOISY UNITS FROM DIFFERENT SOURCES	
<i>Material</i>	<i>Yield</i>
Hog ovaries .....	100 U. per lb.
Hog liver .....	36 U. per lb.
Cow pancreas .....	30 U. per lb.
Cow cotyledons .....	17 U. per lb.
Hog kidney .....	13 U. per lb.
Hog muscle .....	9 U. per lb.
Cow uterus .....	17 U. per lb.
Cow blood .....	40 U. per litre
Sow blood .....	43 U. per litre
Hog posterior pituitary.....	Less than 1 U. per lb.
Hog anterior pituitary.....	Less than 1 U. per lb.
Hog thyroids .....	Less than 1 U. per lb.
Hog spleen .....	Less than 1 U. per lb.
Cow parathyroids .....	Less than 1 U. per lb.
Cow thymus .....	Less than 1 U. per lb.
Steer pancreas .....	Less than 1 U. per lb.
Steer blood .....	Less than 1 U. per lb.
Hen's eggs—yolk .....	Less than 1 U. per lb.
Hen's eggs—white .....	Less than 1 U. per lb.
Vacuum desiccated commercial ovarian residue.....	280 U. per lb.

with 95 per cent alcohol. The extract was filtered off and a second extraction made in the same way. The meat was then discarded. The combined filtrates were distilled in vacuo practically to dryness. The residue was shaken up with 1 litre of ether. This was filtered and 2 litres of acetone added. A precipitate of phospholipins separated which was twice extracted with 1 litre of ether and 2 litres of acetone. The combined ether-acetone filtrates were distilled in vacuo to dryness. The residue was redissolved in ether and filtered. The ether was removed from the filtrate and the material taken up in olive oil for test purposes.

From this table it will be seen that there exists a fairly wide distribution in the animal body of this hormone. The significance of its occurrence in liver and pancreas to a greater extent than anywhere else excepting the ovaries is not clear.

#### PREPARATION OF AQUEOUS SOLUTIONS OF THE HORMONE

Since the injection of oils is frequently accompanied by a type of tumor formation at the site of injection, many attempts were made to render the active principle soluble in water. As a result of these attempts it was found that hydrolysis of the oily residue obtained after removing the ether, as described above, rendered part of the active material soluble in water. This result could be obtained by the use of either acids or alkalis.

Acetic, formic, hydrochloric and sulphuric acids were tried. Acetic acid gave the largest yield in water soluble form. In all cases the technical difficulties of removing the excess acid and then salts was so great that when a sufficient degree of purity had been attained, little was left of the original yield of hormone.

Of the alkalis, sodium hydroxide, potassium hydroxide, barium hydroxide, calcium hydroxide, and sodium carbonate were tried. Normal solutions of these alkalis were used and a comparison made of the yields obtained. After boiling the ether residue for  $\frac{1}{2}$  hour the mixture was quickly cooled. The soap was filtered off and the filtrate neutralized to pH 7.5 and again filtered. The filtrate was taken to dryness in vacuo and extracted with 95 per cent alcohol. The alcohol filtrate was concentrated in vacuo to dryness and taken up in water.

Barium hydroxide gave the greatest yield of crude material but when all the barium was finally removed the resultant yield was low. Sodium hydroxide was found to give the best practical results and was finally adopted as a routine reagent.

The question arose whether or not it was necessary to carry out all the steps of the modified Allen-Doisy process to the final ether residue stage before attempting a hydrolysis. Comparative studies were made at the various stages in the above procedure by treating with sodium hydroxide. It was found that the estrus-inducing hormone could be rendered water soluble at any stage if boiled with the alkali. However, in

some cases mechanical difficulties in handling more than offset any advantage gained. The final procedure for processing ovaries is given below.

One hundred pounds of ovaries were ground in a meat chopper and extracted for 4 hours with 50 gals. of 85 per cent alcohol. The liquid was centrifuged off and filtered. The tissue was re-extracted with 40 gals. of 85 per cent alcohol for another 4 hour period. During both extractions a continuous agitation was maintained. The second extract was centrifuged and filtered. The tissue was then discarded. The combined filtrates were concentrated in vacuo at about 25° C. to approximately 3 gals. This was made up to 85 per cent alcohol and the heavy precipitate so obtained was filtered off and discarded. The filtrate was concentrated to dryness and taken up in ether. The ether solution was allowed to stand at 4° C. for 48 hours and filtered at that temperature. The filtrate was taken to dryness. This was hydrolyzed by using 10 L. of N. caustic soda per 400 gms. of residue. The mixture was brought to a boil and maintained at boiling for 15 minutes. It was then rapidly cooled and filtered through acid washed paper. The filtrate was neutralized to pH 7.2-7.4 and filtered. The filtrate was distilled to dryness in vacuo. The sodium chloride so formed was removed by dissolving the hormone in 95 per cent alcohol and filtering. The alcohol filtrate was distilled to dryness and the residue taken up in water. By this procedure approximately 40 units per lb. of ovaries was obtained.

#### SUMMARY

(1) A study of the occurrence of the estrus-inducing hormone in various animal tissues was made. A fairly wide distribution was found to exist.

(2) A method is described by which the oil-soluble form was rendered water soluble.

(3) A satisfactory procedure is given in detail for the manufacture of the hormone from ovaries.

# A NEW SOURCE OF THE OVARIAN FOLLICULAR HORMONE

J. A. MORRELL, H. H. POWERS AND J. R. VARLEY

From the Biological Laboratories of E. R. Squibb & Sons

NEW BRUNSWICK, N. J.,

Due to the relatively small amounts of the follicular hormone present in the ovary, a rich source which was plentiful and cheap became of great importance if this hormone was to be made available to the medical profession. As reported in the previous paper (1), no other gland was found to contain a large supply. In fact, the circulating blood of an animal was the most concentrated source from which it was obtained.

We found that the fetal fluid of cattle, both amniotic and allantoic, contained large amounts of this estrus-inducing hormone. Further, it can easily be prepared from this material in a water soluble form.

## OCCURRENCE IN AMNIOTIC AND ALLANTOIC FLUIDS

The uterus was obtained from a pregnant cow slaughtered for other reasons. The sacs were dissected away from the cotyledons and each sac was pierced separately and the liquid carefully collected. As judged from the fetus the animal was approximately 5 months pregnant. Two thousand one hundred cc. of amniotic fluid and 1100 cc. of allantoic fluid were so obtained. Both fluids were clear and amber-colored. Identical procedures were followed in each case.

They were mixed with alcohol to give a final concentration of 75 per cent and filtered from a light flocculent precipitate. The extract was concentrated to dryness in vacuo. The residue was an alkaline paste which was neutralized with hydrochloric acid and dissolved in water. A clear solution was obtained. The volume of the amniotic concentrate was 61 cc., and that of the allantoic 48 cc.

These were tested upon spayed white rats according to Allen and Doisy's technique without modifications. The amniotic concentrate tested 3 units per cc., or 87 U. per litre, and the allantoic 2 units per cc., or 87 units per litre. Apparently the distribution is approximately the same in both, and hereafter no attempts were made to keep them separate.

## EXTRACTION AND PURIFICATION

Various attempts were made at the purification of this hormone from the fetal fluid using all the methods previously tried for the preparation of the hormone from other sources. The best procedure so far obtained is as follows:

Ninety gallons of frozen fetal fluid were melted and mixed with alcohol to give 75 per cent concentration. This was stirred for several hours

and then filtered from a protein precipitate. The clear filtrate was concentrated in vacuo to approximately 5 gallons. This concentrate was made up to 50 per cent alcohol and again filtered from a flocculent precipitate. This filtrate was distilled to a thick paste and extracted with 4 gals. of 90 per cent alcohol. A heavy, dark brown, gummy precipitate settled out. The supernatant liquid was decanted and the residue re-extracted with 2 gallons of 95 per cent alcohol. The extracts were combined and ether added to give a concentration of at least 40 per cent. Another gummy brown precipitate settled out. The alcohol-ether solution was decanted and distilled to dryness. The residue was taken up in 2 litres of 95 per cent alcohol and 4 gallons of ether added. A further precipitation occurred. The filtrate was concentrated to dryness and the residue dissolved in water. A small amount of material is insoluble and this was removed by filtering through hard paper. All distillations were carried out in vacuo. All precipitates were discarded. The yield by this procedure varied from 128 units to 200 units per gallon of fetal fluid.

The product so obtained is of a fair degree of purity and is non-toxic. Analysis of a typical preparation in a 10 unit per cc. dilution showed an amino nitrogen value of 0.45 mgm. per cc.; urea nitrogen, 0.84 mgm. per cc.; total nitrogen, 12.46 mgm. per cc.; phosphorus, .134 mgm. per cc., and an ash of 0.45 per cent. This material showed no loss of potency after heating at 125° F. for 32 days. It produced a very slight transitory fall in blood pressure of a dog under amytal anesthesia.

The water solution of the hormone was crystal clear and yellow brown in color. It was non-toxic. As high as 100 units have been given a rat with no effect except to prolong the estrus phase of the cycle. Six hundred and thirty-eight units were administered to a monkey (*Macacus rhesus*) weighing 2.3 kgms. over a period of 6 days with no toxic effect. No local irritation was observed.

#### PHYSIOLOGICAL PROPERTIES

To establish the identity of the estrus inducing substance obtained in this way with the follicular hormone obtained from the ovary, it was felt that at least three other properties should be established, viz., the hastening of sexual maturity in an immature rat, the induction of menstruation in the spayed and immature monkey, and the feminization of a male animal.

#### INDUCTION OF SEXUAL MATURITY IN IMMATURE RATS

As a control, preparations from ovaries, placenta and fetal fluid which had been previously assayed to determine their estrus inducing properties in the spayed rat were administered to immature rats. Solutions were made up to contain 1 unit in 0.2 cc. Injections were given daily until opening of the vagina occurred.

<i>Cage No.</i>	<i>No. of Rats in Cage</i>	<i>Source</i>	<i>Date of Birth</i>	<i>Av. Age of Rat at date of Opening Days</i>	<i>Remarks</i>
1	4	Controls	1-9-28	51	Injection started
2	5	Fetal Fluid	1-9-28	22.5	1-27-28 and con-
3	5	Ovaries	1-9-28	23	tinued until vagi-
4	5	Placenta	1-9-28	22.5	na opened in all
5	4	Controls	1-13-28	54	except controls.
6	5	Fetal Fluid	1-13-28	18.5	1 unit daily

## INDUCTION OF MENSTRUATION IN SPAYED MONKEYS

In another paper (2) we have given in detail the technique and results obtained in the induction of menstruation in both ovariectomized and immature monkeys. In all cases, provided an adequate dosage was administered, menstruation was obtained.

## INDUCTION OF A FEMALE CHARACTERISTIC IN A MALE MONKEY

Various authors have reported that the breasts and nipples of male guinea pigs could be induced to grow and the testes and penis to retrogress by the injection of ovarian follicular hormone. In the female *Macacus rhesus* monkey there is a certain marked secondary characteristic associated with the sexual cycle. The area about the buttocks and extending for several centimeters up the under-side of the tail and down between the legs corresponding to the area occupied by the male scrotum becomes red and swollen during the intermenstrual period, the color and swelling subsiding a few days before menstruation and reappearing a few days after. In the spayed female this same condition may be reproduced by injections of ovarian hormone.

The male *Macacus rhesus* has no periodic cycle and normally manifests no color or swelling of the sexual skin. By the injection of ovarian hormone we were able to induce a reddening and swelling in a male monkey similar to that which occurs in a female. No change could be detected in the nipples or in the testes and penis although the sexual activity of the animal seemed to be diminished, he having been kept with a female during the course of the experiment. The experiment is summarized in tabular form:

Wt., 5 kg. Experiment started 1-16-29.

Date .....	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Units injected...	30	30	30	30		30	30	30	30	30	30		30	30	30
Color of skin...				1			1	1	2	3	3	1	1	2	3
Swelling of skin.							x	x	x	x	x	x	x	x	x

## SUMMARY

1. The ovarian follicular hormone has been demonstrated to be present in the fetal fluid of cows in sufficient amounts to warrant its extraction on a commercial scale and a process has been outlined for its extraction and partial purification.

2. The hormone has been shown to be identical with that extracted from ovary in that it will induce estrus in a spayed rat, menstruation in a spayed monkey and in an immature monkey, hasten the opening of the vaginal orifice in an immature rat and has a feminizing action when injected into a male animal.

Work is being done on the further purification of the hormone, and the establishment of certain of its chemical and physiological properties.

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# Book Reviews

MODERN METHODS OF TREATMENT. Logan Clendening, 1929. With chapters on Special Subjects by H. C. Anderson, J. B. Cowherd, H. P. Kuhn, Carl O. Richter, F. C. Neff, E. H. Skinner and E. R. DeWeese. The C. V. Mosby Company, St. Louis. Pp. 815.

The book includes a 21-page chapter on the use of endocrine products. This is an interesting practical critique on organotherapy by one who is neither an enthusiast nor a nihilist. It is recognized that in properly selected cases excellent results may be obtained and the reason for the many failures that are obtained are discussed. These, as he says, may follow from any one of five as yet uncontrollable causes: "(1) The symptoms present may be due to a dysfunction of the gland, not to either simple deficiency or to simple superabundance of normal secretion; that is, the gland may be pouring out a strange secretion from any produced in health. (2) The methods of administration of the extracts may not be proper. In some instances oral administration may be totally ineffective. For all we know they should be given intravenously. This is not said here in a critical spirit. It is simply a suggestion, the outcome of thinking about my own failures. The proper method of administration of these extracts is still almost totally outside the field of our present knowledge. (3) The product given may be inert. These extracts deteriorate rapidly. We have no good methods of standardization. (4) The symptoms for which the patient is being dosed may not be the deficiency of the gland, the extract of which is being administered, at all. This mistake in diagnosis may be made, in the odor of sanctity—with the best information on our state of knowledge at present. (5) It may be too late. The bodily changes which have occurred may be fixed and use of the gland cannot cause retrogression—examples of this are treating cretinism after the third or fourth year, or Frölich's syndrome after the fifteenth year."

It is interesting to note that the author has the courage to advocate pluriglandular therapy in pluriglandular disorders.

LOS ESTADOS INTERSEXUALES EN LA ESPECIE HUMANA. G. Marañón, 1929. Javier Morata, Madrid. Pp. 262.

For many years the author has been interested in the morphological and functional aspects of sexuality. In this book he has brought together a great many personal observations and supplemented them with material from the literature—with which, incidentally, he shows a catholic acquaintance. Among the interesting topics treated are the conception of intersexuality; morphological aspects of sexuality; classification of intersexual states, such as hermaphroditism, pseudohermaphroditism, gynecomastia, virilism, masculinism, etc.; theories of sexuality, endocrine factors in sexual processes and possible treatment of the conditions. Chapter XX comprises a resume of the significance of virility and femininity in human evolution and in social problems. The thesis that various glands of intersexuality are of common occurrence is ably defended. It is emphasized that all endocrine deviations have a repercussion in the sexual sphere.

The book is well printed and is illustrated with numerous striking photographs. An excellent bibliography is included. The work is worthy of wide attention.

**BODILY CHANGES IN PAIN, HUNGER, FEAR AND RAGE.** Walter B. Cannon, 1929. D. Appleton & Company, New York and London. Pp. 404.

The readers of this Journal need no introduction to this well-known classic. In the fourteen years since the publication of the first edition many more pertinent data, nearly all supporting the original thesis, have been published. These have been succinctly included in the new edition.

The book has been amplified by five new chapters on emotional increase of blood corpuscles, emotional derangement of bodily functions, thirst, two on theories of emotion with the presentation of an attractive alternative to the well-known James-Lange theory.

**INNERE SEKRETION IHRE PHYSIOLOGIE, PATHOLOGIE UND KLINIK.** Julius Bauer, 1927. Julius Springer, Berlin and Wien. Pp. 478.

The subject of endocrinology has become too extensive for detailed treatment in any single volume. The author recognizes this fact and makes no attempt at encyclopedic completeness. The book represents the accumulation and, more important the discarding of years of teaching and clinical experience in this field. It is a book intended to give a judicious survey of the field from the physiological, morphological, pathological and clinical points of view.

The book is clearly written, attractively though not copiously illustrated and well printed. An excellent working bibliography—largely of more recent contributions—is incorporated as a series of foot-notes as in Sharpey-Schafer's well-known book.

The book is worthy of a place among the half dozen best that comes to mind when one desires a general treatment of the subject of the internal secretions.

**THE PIGMENTARY EFFECTOR SYSTEM. A REVIEW OF THE PHYSIOLOGY OF COLOUR RESPONSE.** T. L. Hogben, Biological Monographs and Manuals (Edit. F. A. Crew and W. Cutler) No. 1. Oliver and Boyd. Edinburgh. 1924.

Reviewed in *Endokrinologie*, 3: 239. 1929.

**THE ENDOCRINES IN GENERAL MEDICINE.** W. Langdon Brown, 1927. Paul B. Hoeber, Inc., New York.

Reviewed in *Biol. Absts.* 3: 583. 1929.

**GOITER PREVENTION AND THYROID PROTECTION.** Israel Bram, 1928. F. A. Davis Company, Philadelphia. Pp. 327.

Bram's book is primarily a popular presentation of his well known thesis that exophthalmic goiter is a constitutional disorder much more amenable to medical than to surgical treatment. As such, it is frankly devoted to a considerable extent to special pleading. Whatever may be

the propriety of addressing the lay public on matters upon which medical opinion is so divergent, the mass effect of the book will no doubt be good. It is an effective tract against the evils of "jazz" living.

One must regret, however, the inclusion of a few extreme or dubious statements. It is sweepingly averred, for instance, that no patient with a ductless gland disturbance can become or remain well as a tobacco habitué. Schiff's old experiments—unwittingly on the parathyroid glands—are cited as evidence of the vicious effect of flesh diet in thyroid disorders. In general, the alleged harmfulness of meat eating is overstressed. The carbon dioxide of popular beverages—a substance with which the human body is at all times charged—is noted as harmful.

The book is entertainingly written and is well printed. The sections on practical management of exophthalmic goiter should be particularly valuable not only to lay, but to many medical readers.

The book includes numerous other features, such as discussions of thyroid biology, varieties of goiter, distribution of endemic goiter and goiter prophylaxis. The chapter on endemic goiter is written by Dr. Robert Olesen.

**DISEASES OF THE THYROID GLAND.** Arthur E. Hertzler, 1929. With a chapter on Hospital Management of Goiter Patients by Victor E. Chesky. The C. V. Mosby Company, St. Louis. Pp. 286.

One of the most worth while books on diseases of the thyroid is that of Dr. Hertzler, which now appears in a second edition. It is unique among American works in being based on a thirty years' study of a stable community in which many opportunities have been utilized to observe the evolution of individual cases of thyroid disease. The data thus appears in longitudinal rather than cross-sectional perspective. The writer is an independent thinker with the courage of his convictions and a command of picturesque exposition. The book should receive the close attention of those interested in either the biology or the clinical treatment of thyroid disease.

It is attractively printed and beautifully illustrated with photographs and drawings of original material.

**DIABETES LATENTE.** Felix Puchulu, 1929. Bartolomé Mitre, Buenos Aires. Pp. 213.

Under the direction of and, to some extent, in collaboration with Professor Escudero, the author has made an extensive study of the occurrence, manifestations and treatment of latent diabetes. He speaks for the early recognition of the condition and its treatment under a dietary-insulin régime before it evolves into a more difficult overt diseases.

The technic evolved in Escudero's clinic for the diagnosis of latent diabetes is described and discussed in relation both to numerous personal cases reported and to the recent literature on the topic.

**IODINE IN NUTRITION. A REVIEW OF EXISTING INFORMATION.** J. B. Orr and I. Leitch, 1929. London: His Majesty's Stationery Office. Pp. 108.

Reviewed in J. A. M. A. 93: 871. 1929.

EL METABOLISM BASAL EN LA CLINICA. CON ESPECIAL APLICACION AL DIAGNOSTICO Y TRATAMIENTO DE LAS ENFERMEDADES DE LAS GLANDULES DE SECRECION INTERNA Y DE LA NUTRICION. Mariano R. Castex and Mario Schteingart, 1929. Buenos Aires, Ancieto Lopez. Pp. 239.

Reviewed in J. A. M. A. 93: 871. 1929.

THE ADRENALS: THEIR PHYSIOLOGY, PATHOLOGY AND DISEASES. Max A. Goldzieher, 1929. Macmillan Company, New York. Pp. 436.

Reviewed in J. A. M. A. 92: 1377. 1929.

KEIMDRUSE, SEXUALITAT UND NERVENSYSTEM. O. Kanders. S. Karger, Berlin.

Reviewed in J. Nervous & Mental Disease, 70: 457. 1929.

SYNDROME NEURO-HYPOPHYSIAIRE. D. Guglielmo, 1928. (Institut d'edit. Scient. de Milan.)

Reviewed in Rev. franç. d'endocrinol. 7: 234. 1929.

VUE GENERALE SUR L'ENDOCRINOLOGIE D'APRES 25 ANS DE PRATIQUE. Léopold-Lévi, 1929. Ed. Paul-Martial, Paris.

Reviewed in Rev. franç. d'endocrinol. 7: 322. 1929.

ENDOCRINE DISORDERS. Hans Cursehmänn, 1929. With an introduction by Franz Prange. Oxford University Press, London.

This book is a translation from the German book by the same author, and is designed as a clinical manual based upon a wide personal clinical experience. Within the limited space of 180 pages, the author presents an instructive resumé of the present day practical and theoretical knowledge of the disorders of the glands of internal secretion. The pineal and thymus glands are included in addition to the thyroid, parathyroid, pituitary, adrenals and the gonads. In appendices are described allied conditions, such as mongolian degeneration, dystrophia pigmentosa, myotonia and lipodystrophy. Under diseases of the gonads, Prange gives an interesting and instructive presentation of sexual inversion, hermaphroditism, homosexuality and rejuvenation. The book is well printed, excellently translated and contains numerous photographs from the author's practice.

PHYSIOLOGIE GYNECOLOGIQUE ET MEDECINE DES FEMMES. H. Vignes, 1929. Ed. Masson et Cie, Paris.

Reviewed in Rev. franç. d'endocrinol. 7: 321. 1929.

PNEUMOGASTRIQUE, APPAREIL THYROIDIEN ET ACTIVITE CEREbraLE. D. Sante-noise, 1929. Ed. A. Legrand, Paris. Vol. I, pp. 336.

Reviewed in Rev. franç. d'endocrinol. 7: 320. 1929.

LE PROBLEME DES GLANDES A SECRETION INTERNE. LES PROPRIETES PHYSICO-CHIMIQUES ET PHARMACODYNAMIQUES DES HORMONES. I: L'HYPOPHYSE. II. Peneau, L. Blanchard and H. Simonnet, 1929. Les Presses Universitaires de France. Pp. 249.

Reviewed in J. A. M. A. 93: 1015. 1929.

LA THERAPEUTIQUE PAR LES GLANDES (OPOTHERAPIE). Louis Moinson, 1928. Le François, Paris. Pp. 191.

Reviewed in J. A. M. A. 93: 1016. 1929.

DIE HORMONE IHRE PHYSIOLOGIE UND PHARMAKOLOGIE. Bd. I. KEIM-DRUSEN. HYPOPHYSE. NEBENNIEREN. Paul Trendelenburg, 1929. Julius Springer, Berlin. Pp. 351.

Reviewed in J. A. M. A. 93: 1016. 1929.

STERILIZATION FOR HUMAN BETTERMENT. E. S. Gosney and Paul Popenoe. The MacMillan Company, New York, 1929. Pp. 202.

Over 6,000 sterilizations had been performed in the one state of California prior to January 1, 1929, and the authors have traced the records and results of these sterilizations as far as possible. The first part of the book is devoted to a summary of the author's findings, and the second part to some conclusions to which these findings and a general consideration of sterilizations have led. The authors particularly point out that sterilization destroys no organ or gland of the body, and shows no effect upon sex desire, sex performance, or sex feelings of the subject, thus removing some of the principal objections advanced by opponents of this social and economic measure, so long contemplated and now seriously considered.

Thus the book is of technical interest to endocrinologists only in a negative way. The fact that eugenic sterilization can be carried out without interference with hormone production is of such social importance that this negative aspect is worthy of wide dissemination.

HORMONE AND STOFFWECHSEL. (DIE BEDEUTUNG DER HORMONE FÜR DER STOFFHAUSHALT TIERISCHER U. PFLANZLICHER ORGANISMEN.) [Hormones and metabolism.] W. Raab. Naturwissensch. und Landwirtschaft. 10: F. P. Datterer, Freising-München, 1926. Pp. 195.

Reviewed in Biol. Abstracts, 2: 1590. 1928.

LA NEUROCRINIE HYPOPHYSAIRE. ETUDE HISTOPHYSIOLOGIQUE DU COMPLEXE TUBERO-INFUNDIBULO-PITUITAIRE. Remy Collin, 1928. Gaston Doin et Cie., Paris. Pp. 102.

Reviewed in Biol. Abstracts, 2: 1586. 1928.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch. Bd. II, Lief. III. Curt Kabitsch, Leipzig. Pp. 504. Thomas, E., G. Bayer and G. Zuelzer.

"It is a difficult and thankless task to discuss the physiology of an organ about which so little is positively known," writes Dr. E. Thomas as an introduction to his discussion of the thymus gland. He takes as a point of departure the older work claiming an interference with growth and metabolism in dogs when the thymus is extirpated, but missed the classic paper of Park and McClure showing the mythical character of the thymic factor. He agrees, however, that the organ can be extirpated without lasting harm. The evidence of inter-relationships between the thymus, thyroid and sex glands is recognized. While the literature cited is predominantly German, a considerable number of papers in other languages is noted. The article runs to 44 pages.

The next 390 pages comprise a discussion by Professor G. Bayer of the physiology of the adrenals. The treatment of the subject is admirable throughout. It shows wide acquaintance with the literature and keen critical judgment—a quality very necessary in dealing with a subject so replete with contradictions. Space does not permit an analysis of the article in detail. Suffice it to say that anyone desiring a well-balanced, readable discussion of adrenal physiology can profitably turn to this one. The well chosen bibliography runs to 33 pages.

Professor G. Zuelzer closes the volume with brief discussions of the endocrine functions of the salivary glands, stomach, intestines, liver and spleen.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch, Bd. III, Lief. I. Curt Kabitzsch, Leipzig. Pp. 201. Deusch, G., H. Curschmann, E. Wieland and F. Siegert.

Professor G. Deusch treats together, under the caption "Hyperthyroses" the various disorders in which overactivity of the thyroid gland is a prominent feature. While no attempt is made in an article of 70 pages to deal exhaustively with the subject, such outstanding topics as have become classic in such treatises are covered in an interesting way. The literature reviewed is well selected to exemplify the best thought at this time.

Professor Hans Curschmann devotes 27 pages to a discussion of hypothyroidism in adults and 8 pages to an appendix dealing with Chaga's disease and adiposis dolorosa. The section is notably incomplete. The last section is the best.

A creditable and well illustrated article by Dr. E. Wieland of Basel deals with hypothyroidism in children (44 pages) and an equally satisfactory article (53 pages) by Professor F. Siegert sets forth the outstanding knowledge of athyroses in children.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch. Bd. III, Lief. II. Curt Kabitzsch. Pp. 386. Josefson, A., B. Aschner, E. Thomas, R. Ehrmann, L. Dinkin, O. Herschan, F. C. Geller, A. Hermstein, G. Hirsch and L. Fraenkel.

Dr. A. Josefson of Stockholm discusses somewhat briefly the diagnosis of acromegaly and gigantism, dystrophia adiposo-genitalis and Simmond's disease. A few unenthusiastic remarks on treatment conclude the chapter. The article is notable for its original illustrations. The bibliography is incomplete in content and in form, but is well selected.

In an article of 27 pages, Dr. B. Aschner gives an excellent presentation of what information is available on diseases of the pineal gland. The author demonstrates his command of the world's literature.

Dr. E. Thomas reviews a few of the German papers on clinical aspects of thymus deficiency (9 pages).

One of the notably satisfactory chapters of the series is that of Drs. R. Ehrmann and L. Dinkin on the clinical pathology of the adrenals. Acute and chronic Addison's disease, hyperfunction of the medulla and of the cortex are separately treated. The bibliography is unusually complete and is up to date.

Developmental disorders related to ovarian functions as portrayed in the German literature are discussed by Dr. O. Herschan (40 pages).

From a like point of view, Dr. F. R. Geller treats of sexual and kindred functional disturbances of women (46 pages).

In a similarly narrow way, Dr. A. Hermstein deals with disturbances of pregnancy (47 pages), and Dr. G. Hirsch with the mammary glands in relation to internal secretion (28 pages).

Finally, Professor L. Fraenkel has brought together some unusual German medical lore on the effects of endocrine neoplasms on the genital apparatus. Among the illustrations are four beautifully reproduced in colors (32 pages).

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch. Bd. III, Lief III. Curt Kabitzsch, Leipzig. Pp. 248. Klose, H., G. Büttner and H. Eggenberger.

This volume comprises two chapters on thyroid deficiency. In the first, Drs. Klose and Büttner discuss the subject of cachexia thyreopriva (strumipriva). The first sections include a historical discussion of the results of thyroid extirpation in men and animals with reproductions of numerous illustrations from the classic contributions, the cause of the disorder and the end results in various organs. The section on results in animals is especially interesting. The numerous other topics that conventionally go to make up a chapter of this kind are in general well treated. An admirable bibliography completes the chapter, though one notes with surprise the absence of any reference to Halsted's work.

Dr. Eggenberger discusses goitre and cretinism at length, utilizing the rich material of Switzerland for illustration, though the goitre belts of the entire world are surveyed. The geographical, morphological and chemical aspects of the goitre problem are well treated, as is the matter of prophylaxis. The article is completed in the next succeeding volume of the series. The illustrations are notably good. Spatial limitations do not permit detailed note of all the many excellences of the chapter. It closes with a good bibliography of the world's best contributions.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch. Bd. III, Lief IV. Curt Kabitzsch, Leipzig. Pp. 445. Eggenberger, H., G. Peritz, E. Leshke and W. Cimal.

In addition to the closing part of Dr. Eggenberger's chapter on goitre and cretinism previously noticed, this volume includes a 60-page discussion of the parathyroid by Dr. Peritz, one of 164 pages on disturbances of the autonomic nervous system by Dr. Leshke, and one of 102 pages by Dr. Cimal on endocrine factors in the psychoses and neuroses. The two latter are derived very largely from German sources and are of correspondingly limited authority.

HANDBUCH DER INNEREN SEKRETION. Ed. M. Hirsch. Bd. III, Lief VI. Curt Kabitzsch, Leipzig. Pp. 273. Pulvermacher, L., M. Rosenberg, A. v. Szily, F. Poos and P. Krantz.

The volume is made up of a discussion of the possible endocrine function of the skin by Dr. Pulvermacher, of diabetes by Dr. Rosenberg, of internal secretions and the eye by Drs. v. Szily and Poos, and internal secretions and dentistry by Dr. Krantz. The volume is largely devoid of illustrations and the sources are largely German.

# Abstract Department

Adrenalin in malaria. Aguilar, R. *Ann. Int. Med.* 2: 1343. 1929.

The author injects 8-15 minims of adrenalin chloride when quinine is administered for pernicious malaria. Nine cases are reported in which this mode of treatment was successful.—E. L.

The suprarenal glands and hypertension: A study of the veins within the suprarenal glands. Allen, E. V., *Ann. Int. Med.* 3: 153. 1929.

Veins of the suprarenal gland, the individual areas of the lumens of which in cross sections are between 19.9 and 30.0 sq. mm. have, in cases of hypertension, a ratio of muscle to lumen twice as great as that in cases of normal blood pressure. Theoretically, this hypertrophy indicates the following: (1) increased function of the suprarenal glands, (2) overactivity of the sympathetic nervous system, or (3) the effect of noxious substances in the blood stream. The total area of the lumens of all veins, as defined in the paper, is greater in cases of hypertension than in cases of normal blood pressure. This shows that there is a higher degree of vascularization in the former which probably indicates a higher level of functional activity. These observations are distinct evidence of a close relationship between increased functional activity of the suprarenal glands and hypertension.—Author's Abst.

The clinical symptoms and laboratory data in the diagnosis of Addison's disease (Los sintomas clinicos y los datos del laboratorio en el diagnostico de la enfermedad de Addison). Bonilla, E., *Guipúzcoa Médica*, No. 141, 43, 1928.

The diagnosis of atypical disease may be very difficult if one regards only the classic symptoms. The author discusses the inconclusiveness of skin pigmentation as well as its typical manifestations. Blood examinations give more significant data. In this disease one generally encounters leucopenia, lymphocytosis, reduced blood sugar and cholestrin and depression of the alkaline reserve. The most valuable single datum is accelerated segmentation time of the red cells. This is found constantly and appears early in the course of the disease.—G. M.

Experiments with adrenaline. Burrige, W. and D. N. Seth, *Quart. J. Physiol.* 19: 14. 1929.

This is a report of the effects of adrenaline on the frog heart perfused with low-calcium Ringer solution. It was found that the drug, in all dilutions, was augmentory, but there was also an independent depressing action, the altered contraction height representing a balance between two opposing effects. Adrenaline affects acceleration of the change from systole to diastole, apparently by shortening the refractory period and thus giving the depressing effect. The particular results obtained in a given experiment depend on existing conditions at the time, such as the cardiac reserve and the conditions demanding cardiac response.—C. I. R.

Regenerative power of adrenal tissue (Essais de régénération des tissus surréniaux). Celestino da Costa, A., *Compt. rend. Soc. de biol.* 100: 517. 1929.

In rabbits one adrenal was removed entire and later most of the remaining gland. Even after two months the portion in situ showed no evidence of regeneration.—J. C. D.

On the adrenalin content of the suprarenal capsules in experimental traumatic shock (Sul contenuto in adrenalina delle capsule surrenali nello shock traumatico sperimentale). Dogliotti, A. M. and G. Giordanengo, *Ann. ital. di chir.* 8: 391. 1929.

A fall of blood pressure is a constant and fundamental symptom in the morbid picture of traumatic shock. It is known that increased adrenalin output follows a violent painful stimulus. Also, in the pressure curve of experi-



mental traumatic shock there is observed after a reflex rise a secondary rise in arterial pressure, which continues 15 or 20 minutes. This phenomenon has been interpreted as a consequence of the excessive production of adrenalin in the first period of shock. In suprarenalectomized dogs the pressure curve lacks this secondary rise. This study was undertaken to determine, by means of quantitative determination of the adrenalin content of the suprarenal glands, their behavior in the presence of severe trauma. Insufficiency of the suprarenals consequent to an initial excess of function is suggested as a part of the later picture. Guinea pigs were used. The suprarenal glands were removed, extracted, and the adrenalin content was determined by the method of Battelli, by that of Folin, Cannon and Denis, and by injecting the extracts into a rabbit's jugular vein and measuring the arterial pressure. The extracts of fresh gland and to a less degree the extracts of dried gland from the animals which had undergone the most severe experimental trauma (evisceration, multiple fractures associated with tearing of the sciatic nerves) showed a constant diminution of the adrenalin content, evident one hour after the trauma and of greater degree after 6 to 8 hours. The extracts of the suprarenals from animals undergoing simple tearing of one sciatic or simple fractures of the limbs showed little differences in adrenalin content. The maximum diminution in adrenalin content observed from 6 to 8 hours after the greatest trauma was estimated to be from one-half to one-third of the content of the gland of normal animals. The two methods of estimation used (colorimetric and biological) gave corresponding values.—L. C. Wyman.

Suprarenal apoplexy as the cause of an extensive perirenal haematoma (*Apoplexie de la glade surrénale causée par un hématome périrénal étendu*). Fedinec, Bratisl. lekár. listy, 9: 108. 1929.

The author has observed a case of unilateral suprarenal apoplexy. The patient was a badly nourished woman of 35 who, while walking, was attacked suddenly with a violent pain in the right lumbar region, associated with vomiting and persistent sensation of pressure in the right hip. On post mortem hemorrhage into the right suprarenal capsule was found, the cause of which could not be determined by microscopic examination of the organ.

—Author's Abst.

The action of strychnine upon the denervated heart and upon the secretion of adrenalin. Hormon, P. M. and C. M. McFall, J. Pharmacol. & Exper. Therap. 37: 131. 1929.

In decerebrated cats with denervated heart, but with adrenal and liver innervation intact, strychnine does not directly increase the output of adrenin. Morphine has no effect on the denervated heart if the adrenals are tied off. If the latter are intact, there is a marked and sustained acceleration. It is believed that this is due to increased secretion of adrenin.—C. I. R.

On adrenal pathology (*Zur Nebennierenpathologie*). Kovacs, W., Beitr. z. path. Anat. u. z. allg. Path. 79: 213. 1928.

Eight cases showing bilateral lesions of the adrenals are fully reported and discussed chiefly from their pathological and physiological aspects. The classification adopted and the grouping of the cases is as follows: Cytotoxische schrumpfnebenniere, 1 case; vaskuläre schrumpfnebenniere, 3 cases; tuberculosis of the adrenals, accessory adrenals, etc., 4 cases. In the case of simple atrophy the regenerated nodules of cortical tissue suggested a similarity with cirrhosis of the liver. The toxin responsible for the adrenal damage may be endogenous and haematogenous, and the atrophy being bilateral emphasizes this as a possibility. Observations in post mortem and experimental material have shown the cortex to be essential to life while destruction of the medullary chromaffin tissue can be compensated for by hypertrophy of a similar tissue in the sympathetic system. When only the cortex of one gland has been destroyed, compensatory hypertrophy occurs in the surviving gland and no evidence of the Addisonian syndrome results. In one case of the series cortical regeneration was slight and yet the patient survived for a considerable time. Incomplete cortical destruction even if very severe will not result in an acutely fatal termination. Although the cortical lesion may be essential in the production of Addison's disease yet medullary damage must also play a part. But medul-

lary lesions alone are of little significance. On the whole the results of this investigation lead the author to believe that the organ as a whole was involved in Addison's disease. As for the relationship between cortex and medulla interaction is essential as suggested by their vascular supply. The cortex and medulla each have an afferent artery but only the medulla possesses an efferent vein. The cortical blood in passing through the medulla must add its contribution to the medullary secretion before the adrenal product reaches the body generally. For this reason medulla without cortex cannot function effectively.

—William Susman.

Histamine and adrenalin in relation to salivary secretion. Mackay, Margaret E., *J. Pharmacol. & Exper. Therap.* 37: 349. 1929.

Histamine did not give a constant effect on salivary secretion in cats and dogs and in those experiments in which there was no response, blood pressure records showed a fall followed by a rise instead of a continuous depressor response. After removal of the adrenals a uniformly increased secretion was obtained and no rise in blood pressure. Continuous slow intravenous injection of dilute adrenalin after removal of the adrenals, was followed by histamine injection with poor secretory response. The results are interpreted as indicating increased secretion of adrenalin after histamine and an antagonism between the two substances.—C. I. R.

On the pathogenesis of serious symptoms of suprarenal insufficiency (*Sur la pathogénie des accidents graves de l'insuffisance surrénale*). Maraño, G., *Presse méd.* 63: 1021. 1929.

This paper presents a discussion of hypoglycemia and of acidosis in suprarenal insufficiency, both from the clinical and from the experimental viewpoint. The author's contributions were based upon the observation of 104 cases of Addison's disease in all its forms, in 15 of which he had been able to make an anatomical and pathological study. The serious symptoms of suprarenal insufficiency may be classed in three groups: sudden death, digestive symptoms which resemble cholera, peritonitis or appendicitis, and nervous symptoms such as psychopathic, meningitic, myoclonic, and convulsive or comatose. A disturbance of carbohydrate metabolism is present in Addison's disease. There may be an actual hypoglycemia or a latent hypoglycemia which may be demonstrated by the use of insulin or by other means. In organisms with spontaneous or experimental suprarenal insufficiency there is a tendency to acidosis. This acidosis is more serious when definite symptoms of the digestive or encephalopathic type appear and develops parallel with these symptoms. This leads to the conclusion that acidosis is important in the pathogenesis of certain of the symptoms of Addison's disease, but does not exclude other factors such as hypoglycemia, hyperviscosity, other intoxications, etc. The acidosis in Addison's disease appears to be concerned with the disturbance of carbohydrate metabolism, which is of a type opposite to that in diabetes. It does not appear to be comparable to nephritic acidosis. After the injection of glucose in cases of Addison's disease symptoms of acidosis appeared. This is in accord with certain experimental work in animals. The exact mechanism of this acidosis is not determined, but certain experimental work indicates that hepatic insufficiency may play a part. There may be hepatic insufficiency in Addison's disease. Antiacidotic treatment is therefor indicated to combat the symptoms mentioned.—L. C. Wyman.

Primary and secondary adrenal insufficiency (*Insuficiencia suprarrenal primitiva y secundaria*). Maraño, G., *Medicina Latina*, 1: 4. 1929. Also *Rev. Españ. de med. y cir.* 12: 11. 1929.

Adrenal insufficiency presents two types with intervening grades that are of interest from the standpoint of both pathogenesis and prognosis, namely, the primary and secondary forms. Many cases of Addison's disease are seen in which there is evidence of an underlying constitutional factor. They show general hypoplasia, tendency to infantilism and to status thymicolymphaticus. This constitution is believed to be a result of congenital adrenal insufficiency, which lowers the resistance to tubercular infection. This constitutional hypoplasia may explain the great frequency of Addisonian manifestations in Spain. The secondary cases are those in which there is no constitutional liability to

infection, the adrenals being involved more or less incidentally. It is interesting to note that in the primary forms melanoderma is likely to appear late and to be slight in degree in comparison with other symptoms; in the secondary types it is likely to appear early and to be intense. The prognosis is much more grave in the primary type.—E. B.

**Muscular lactic acid in suprarenalectomized rats** (*El ácido láctico muscular en las ratas suprarrenoprivas*). Mazzocco, P., *Rev. Soc. argent. de biol.* 4: 1. 1928. Also *Compt. rend. Soc. de biol.* 99: 174. 1928.

Rats were attached to a board, the vertebral column was sectioned, and the caudal end of the cut spinal cord was stimulated by means of a faradic current of such a strength that the hind legs were rigid in tetany for one minute. At this point one hind leg was ligated, the muscles extirpated and frozen between two plates of glass. The muscles of the other leg were extirpated after  $\frac{1}{2}$ , 1, 2, 3 or 4 minutes. Lactic acid was determined by a method similar to those of Meyerhoff and of Embden. The average amount of muscular lactic acid, after tetanization of one minute, was greater in three lots of suprarenalectomized rats than that in three lots of controls. The determinations were made 10, 30 and 60 days after operation. The rate of decline of the amount of lactic acid following the period of tetanization did not bear a regular relation to the time of rest, but in general the recuperation was a little better in the controls than in the suprarenalectomized rats.—L. C. Wyman.

**The use of adrenalin in its effect on basal metabolism in the diagnosis of latent hyperthyroidism** (*Del estudio de los efectos de y en especial al de los hipertiroidismos latentes*). Micó. *Arch. d'Endocrinol. y Nutricion*, 2: 49. 1927.

Injection of a half milligram of adrenalin in normal subjects produces a slight increase in the basal metabolic rate. In hypothyroid subjects it produces a lesser effect or none. In typical hyperthyroidism the basal metabolism although initially high promptly increases more than 30 per cent after the injection of adrenalin. There is a group of cases of latent hyperthyroidism in which the clinical picture is obscure, and the basal metabolism is within normal limits, but in which the injection of adrenalin produces a sudden elevation of the basal rate. This fact is of diagnostic value. This is particularly true of cases in which thinness is the only notable manifestation of the disorder. The reaction permits an easy differentiation between neuroses that give manifestations similar to hyperthyroidism and true latent hyperthyroidism. The reaction is also of value in gauging the treatment of thyroid insufficiency. It discloses the onset of masked therapeutic hyperthyroidism.—E. B.

**Effects of intravenous injections of adrenin on tired muscle** (*Action de l'adrénaline en injection intraveineuse sur les muscles fatigués*). deMira, F. and J. Fontes, *Compt. rend. Soc. de biol.* 101: 976. 1929.

Injections of dilute solutions of adrenin reduced the fatigue in rabbit muscle. The effects of the injection were prolonged to 45 minutes. The salutary effects of various cortical extracts may be due to very minute traces of adrenin present in them. To test this, very dilute solutions of adrenin were examined for their power to relieve the fatigue in the flexor muscle in the rabbit's foot, tired by electrical stimulation. Dilutions of .0016 mgm. per kilo of body weight were effective, .016 mgm. was most efficient, and doses of .02 mgm. and over were deleterious. The increase in power of contraction was very striking and lasted for more than an hour. The result is ascribed to capillary dilatation.—J. C. D.

**The effects in two clinical cases of unilateral extirpation of the adrenal glands** (*Estudio de la función suprarrenal en dos casos de extirpación unilateral de esta glándula*). Morros Sarda, J. and A. Moya Gaston, *Med. iberica*, 1: 729. 1928.

Following unilateral extirpation of the adrenal glands from two epileptic subjects the authors noted moderate variations in the blood sugar, blood cholestrin, and alkaline reserve. The most significant change was in the red cell sedimentation time, which was increased respectively from 3 and 2 mm. per hour to 46 and 59. These results confirm the opinion of Bonilla and Moya that this is a valuable diagnostic datum in cases of adrenal insufficiency.—E. B.

**Suprarenal cortical extracts in suprarenal insufficiency (Addison's disease).** Rogoff, J. M. and G. N. Stewart, J. A. M. A. 92: 1569. 1929.

The authors report promising results from the use of an adrenal cortex preparation by mouth in 7 cases of adrenal deficiency. The nature of the extract is not disclosed.—R. G. H.

**The part played by the adrenal cortex in development of cancer (Rôle du cortex de la surrénale dans le développement du cancer).** Sokoloff, B., *Compt. rend. Soc. de biol.* 101: 264. 1929.

Marked enlargement of the adrenal gland takes place in chickens suffering from the Rous sarcoma, and a distinct but less striking change in mice with Bashford's carcinoma. The changes in the cortex include dedifferentiation followed by degeneration.—J. C. D.

**Studies on suprarenal insufficiency V. The non-protein nitrogen and urea in the blood of suprarenalectomized rats.** Wyman, L. C. and B. S. Walker, *Am. J. Physiol.* 89: 349. 1929.

Following double suprarenalectomy in rats the non-protein and urea nitrogen of the blood may be increased, the amount of increase tending to parallel the severity of the symptoms of suprarenal insufficiency. Such increases were not noted in rats having either gross accessory cortical tissue or successful cortical transplants, in the absence of demonstrable chromaffin tissue. Following control blank operation infrequent, moderately high values for both substances were found during the first two weeks after operation, but these values were not as high as those observed in suprarenal insufficiency. Otherwise the values obtained were normal. The results indicate that the high values for non-protein and urea nitrogen of the blood observed after suprarenalectomy are associated with cortical insufficiency. It is suggested that this is further evidence for a function of the suprarenal cortex concerned with the steady maintenance of certain bodily conditions.—Authors' Summary.

**Studies on suprarenal insufficiency VI. Anaphylaxis in suprarenalectomized rats.** Wyman, L. C., *Am. J. Physiol.* 89: 356. 1929.

Of a group of 25 doubly suprarenalectomized rats sensitized with horse serum 36 per cent died from anaphylactic shock following the test dose, 20 per cent had severe symptoms, 12 per cent had moderate symptoms, and 32 per cent had slight symptoms. No correlation was found between the presence or absence of gross accessory cortical tissue or the time of survival after operation and the susceptibility to anaphylactic shock. A group of 29 normal rats sensitized with horse serum had, following the test dose, no symptoms or only slight or moderate symptoms. Of 15 of these rats which were suprarenalectomized after the test injection 12 died of anaphylactic shock following a second test dose injected after operation. Of 15 suprarenalectomized rats having autoplasmic cortical transplants, and in some cases gross accessories as well, 40 per cent died from anaphylactic shock following sensitization and the injection of a test dose of horse serum. An attempt to reduce the susceptibility of suprarenalectomized rats to anaphylactic shock by means of injections of adrenalin chloride solution gave suggestive though incomplete evidence of possible protection from this source. It is concluded that suprarenalectomized rats are more susceptible than normal rats to anaphylactic shock, and that this increased susceptibility is not related to cortical insufficiency, but that it is consequent to the lack of medullary suprarenal tissue.—Author's Summary.

**Studies on suprarenal insufficiency VII. Note on temperature regulation in suprarenalectomized rats.** Wyman, L. C. and Caroline Tum Suden, *Am. J. Physiol.* 89: 362. 1929.

After two hours in a moderately cold room normal rats, suprarenalectomized rats with autoplasmic cortical transplants, and suprarenalectomized rats having gross accessory cortical masses (with two exceptions) have similar slight variations in the rectal temperature. All these have no marked external reactions to the cold and recover their original normal temperature after one hour at room temperature following exposure to cold. Rats having cortical

insufficiency show a fall in the rectal temperature after two hours in the cold room, show more or less marked external reactions to the cold, and do not recover their original temperatures in a warm room as soon as those having cortical tissue. The fall of rectal temperature upon exposure to cold and the inability to rapidly recover normal temperature is correlated with the degree of cortical insufficiency which is present. It is concluded that the suprarenal cortex, as well as the medulla, is indirectly concerned with heat regulation.  
—Authors' Summary.

**Sudden death and glands of internal secretion** (*Muerte subita y glandulas de secrecion interna*). Bonilla, E., *Rev. Ib.-Am. de Cienc. med.* 3: 231. 1928.

The author discusses at length the significance of endocrine factors in vulnerability. The article does not lend itself to abstracting.—R. G. H.

**Standardization of biological products.** Burn, J. H., *Internat. Clin.* 3: (Series 39) 15. 1929.

Among other things the author calls attention to the biological assay of insulin, pituitary extract and ovarian hormone. The original definition of the unit of insulin was the amount required to cause the blood sugar of a normal fasting rabbit (weighing 2 kgm.) to fall to the value of 0.045 per cent. Soon it was discovered that this unit was extremely variable. A common standard of reference was therefore called for and the assay of insulin became comparative. The modified procedure now amounted to the examination of an unknown sample and its comparison with the standard to find out how much stronger or weaker the former might be. Until 1928 there was no available proof that the potency of pituitary extract as measured by its oxytocic property on the guinea pig represented its potency for obstetrical purposes. That oxytocin is responsible for contraction of the human uterus has now been proved, while Bourne and Burn have found that vasopressin is devoid of any uterine effect. Recently it was shown that an estimate of the oxytocic property does not offer a trustworthy guide to the amount of pressor and antidiuretic constituents. There is at present no satisfactory animal method of measuring the antidiuretic effect. Experiments on rats have yielded evidence of the potency of ovarian hormone prepared in 1923 by Allen and Doisy. The unit of ovarian hormone was described as the least quantity sufficient to cause oestrus in an ovariectomized rat of 140 gm. weight. This definition was later modified by Coward and Burn, who redefined the unit as the amount of hormone required to produce oestrus in 50 per cent of rats, which made ample allowance for variation of response in experimental animals. The author calls attention to the need, in biological assay, of careful consideration of individual variations in response to the substance assayed, whether it be a matter of laboratory animals or the human patient.—I. B.

**Blood sugar studies on children with endocrine dysfunctions, using the author's micro Folin-Wu method of quantitative blood sugar estimation.** Byrd, T. L., *South. M. J.* 22: 729. 1929.

Blood sugar determinations were made on the following types of endocrine cases: cretins, 4; mixed mongol-cretin, 3; hypothyroid, 1; obesity with hypopituitary, hypothyroid, and hypogonad, 7; anterior pituitary deficiency, 3. Some received treatment while others did not. The results obtained were not constant and could not be related; high tolerance was found with treatment and in the absence of treatment. The author concludes that blood sugar tolerance tests are of no special value in differentiating hypofunctioning endocrine glands. Treatment does not seem to alter the blood sugar content to any great degree.—M. B. G.

**Operative treatment for atrophic or poorly developed endocrine glands by implantation of a new arterial circulation.** Goljanitzki, I. A. and A. I. Obolenskaja, *Arch. f. klin. Chir.* 154: 623. 1929.

The authors believe that treatment of endocrine deficiency by the known methods, viz., organotherapy, homo- and heteroplastic transplantation and ligation of the excretory ducts of mixed glands, fails in such cases as eunuchoidism, infantilism, etc., because these conditions are primarily disorders of the central or sympathetic nervous system or the blood circulation in relation to the

affected glands. The authors have obtained evidence both by animal experimentation and clinically in man that by supplying such atrophied or aplastic glands with a new arterial circulation and a new innervation it is possible to favorably influence or restore function. The sex glands of rabbits, which were cut off from their nutritive circulation were saved from necrosis by the implantation of the spermatic artery into the testis in the male and of the artery of the ligamentum lata into the ovary in the female. A new vessel plexus was observed to have been formed in the place of implantation. The operation with eunuchoids consisted in implanting the proximal stump of the inferior epigastric artery into either the split atrophic testis or the spermatic cord and suturing the lumboinguinal nerve to the spermatic nerve. In a myxedema tuberosum patient a stump of the right lingual artery was implanted into the right lobe of the atrophic thyroid.—N. K. Schaffer.

**A new circulatory hormone. Second report (Über ein neues Kreislaufhormon. II. Mitteilung).** Kraut, H., E. K. Frey and E. Bauer, *Ztschr. f. phys. Chem.* 175: 97. 1928.

A substance has been isolated from normal urine (by precipitation with uranyl acetate and subsequent absorption on infusorial earth) which will cause a definite increase in pulse amplitude lasting for a minute when injected into a dog in half milligram doses. A less pure preparation has been obtained from the blood, 60-80 cc. of blood yielding 140 mgm. of a preparation equaling in activity 0.5 mgm. of the urine preparation. Blood serum has the effect of inactivating the circulatory hormone after a period of minutes or hours, this inactivating action being destroyed by heating, acidification, addition of alcohol, filtration with infusorial earth, or digestion with papain. Following digestion with papain and dialysis, a unit of the active material may be obtained from as little as 2 cc. of blood. The hormone is differentiated from histamine by having an opposite effect on the liver volume and carotid pressure.

—Burnham S. Walker.

**Condition of endocrine organs in rickets and spasmodophilia.** Stoltenberg, L., *Norsk. mag. f. laegevidensk.* 90: 729. 1929. *Abst., J. A. M. A.* 93: 1036.

In rabbits with rickets and spasmodophilia, Stoltenberg did not find morphologic changes in the suprarenals or thymus of etiologic or pathogenic significance. In the thyroid and parathyroids, hyperplasia and hypertrophy were noted and interpreted as signs of increased internal secretion. While no etiologic or pathogenic responsibility in the usual sense is ascribed to these organs, the rachitic and spasmodophilic picture is influenced by their reactions.

**Reactions of immature monkeys (*Macacus rhesus*) to injections of ovarian hormone.** Allen, E., *J. Morphol.* 46: 479. 1928.

Series of injections of ovarian hormone have been made into normal and ovariectomized immature animals. Injections were made twice daily for twenty-two days. The total dose exceeded 1000 rat units per animal. Effects noted in the living animals were the appearance of reddening and swelling of the "sexual skin" and change of the cell content of the vaginal smear to the interval type of the mature animal. Measurements made at operation, before and after injections, indicated considerable enlargement of both the cervix and body of the uterus. The thymus glands of the injected animals weighed significantly less than those of the controls. Histologic study of the genital tract showed extreme thickening of the vaginal walls, considerable growth of the uterine epithelium and glands, hypertrophy of the muscle layers of the uterus, and advanced differentiation of the epithelium of the uterine tubes. The ovaries of the injected normal animal were smaller and contained fewer primordial and medium-sized follicles than those of the controls. The presence of large numbers of atretic follicles, especially large flattened scars from former relatively well-developed follicles also suggests a harmful effect of this amount of ovarian hormone upon follicular development. Several stages of elimination of ova from polyovular follicles were also observed. There was marked growth in the ducts and an increase in the number of alveoli of the mammary glands.—Author's Abst.

Further experiments with an ovarian hormone in the ovariectomized adult monkey, *Macacus rhesus*, especially in the degenerative phase of the experimental menstrual cycle. Allen, E., *Am. J. Anat.* 42: 467. 1928.

In previous experiments with active extracts of pig ovaries and human placenta, standardized quantitatively by the oestrous test in spayed rats, the reaction of ovariectomized mature monkeys was studied. The animals sacrificed in this first series were killed immediately after the last of a series of injections. The present experiments were a continuation of this work and dealt especially with retrogression in the sexual organs during the five days following the cessation of injections, the animals being killed on the first, third and fifth days after the last injections when the effects of hormone stimulation were retrogressing. Measurements of uteri showed considerable decrease in diameters by the third day and a further decrease (almost to the size of the controls) by the fifth day after the last injection. The lumen of the vagina of each animal contained masses of sloughed epithelial cells. Leucocytic infiltration of the stroma of the vaginal wall had begun by the third day and spread to the basal layers of the epithelium by the fifth day, but leucocytes had not entered the masses of epithelial cells in the lumen. Marked migration of leucocytes through the cervical glands, as described in earlier experiments, was noted in all animals. The uterine mucosa of the animals killed on the first and third days after the last injection was pale, spongy and edematous. That of the monkey killed on the fifth day was in an early menstrual stage. There was menstrual discharge in the lumen of the uterus and vagina and the endometrium was hemorrhagic. Histologic section showed a typical menstrual endometrium. Cessation of growth was indicated by a low incidence of mitosis. The edematous condition had also subsided by the fifth day after the cessation of injections. The last case added to earlier experiments makes a total of eight experimental menses in ovariectomized monkeys following withdrawal of hormone stimulation after considerable periods of injections.—Author's Abst.

Sympatheticotrophic cells in the ovary and their function (*Sympathikotrope Zellen im Eierstock und ihre neurokrine Funktion*). Berger, L., *Virchow's Arch. f. path. Anat.* 267: 433. 1928.

In 218 pairs of ovaries 168 contained sympatheticotrophic cells in small groups or in masses of 100. Frequently they were intrapara- or peri-neural in distribution. Generally they were round or polyhedral, somewhat smaller than ganglion cells, possessed a round nucleus with 1 or 2 nucleoli, an eosinophilic cytoplasm which frequently contained brown pigment, and occasionally the cytoplasm was vacuolated. Ten per cent contained cytoplasmic, eosinophilic crystalized bodies usually cylindrical in shape. In the testicle similar cells are associated with the interstitial cells of Leydig and show corresponding distribution and changes. This may indicate an associated internal secretory function for the sympatheticotrophic cells. By analogy a similar function for the sympatheticotrophic cells of the ovary is possible.—Wm. Susman.

A case of macrogenitosomia and intersexuality of gynecomastic type (*Contribución al estudio de la macrogenitosomía, con descripción de un caso de síndrome macrogenitosómico, e intersexualismo puberal de tipo ginecomástico*). Bonilla, E., *Arch. españ. de pediat.* 12: 591. 1928.

A case of this disorder in a twelve-year-old child is described, with citation of 78 pertinent articles from the literature. The theoretical possibilities of the endocrine etiology are discussed.—R. G. H.

Effect of castration on the bones of the nose (*Influence de la castration sur les cornets du nez*). Campy, C. and N. Kritch, *Compt. rend. Soc. de biol.* 100: 413. 1929.

In guinea pigs, rabbits, sheep, and cattle, castration is followed by an atrophy or failure in growth of the bones of the nose.—J. C. D.

Chemical sympathectomy of the spermatic cord (*Simpatectomía química del cordón espermático*). Cassuto, A., *Rev. españ. cir y urol.* 8: 351. 1926. Abst., *Biol. Absts.* 3: 583.

After reviewing the literature and concluding that the interstitial tissue of the testicle is probably not the source of hormonal activity, the author de-

scribes experiments on 18 dogs. The spermatic cord was exposed by an inguinal incision and its arteries painted with a solution of phenol for 2 cm. This treatment, which is supposed to destroy the fibres of the sympathetic nerves surrounding the arteries, resulted in an increase in size of the arteries, increased blood supply to the testicle, and, as shown by histological examination up to nine months later, increase in the size of the testicle and in the activity of the seminiferous tubules, without noticeable change in the interstitial tissue. The dogs showed improved vigor and energy and increase of libido. Similar results were obtained by operation on the ovarian arteries of 3 bitches. The author then performed the same operation (unilaterally) on 6 young men who were suffering from sexual debility; the longest period of observation since is 8 months. In every case the patient reported improved physical and mental condition and complete restoration of sexual function.

The treatment of ovarian deficiency with intravenous injections of an ovarian extract (*Die Behandlung der Eierstockernühdungs-Erscheinungen mittels intravenöser Eierstockertrakt Injektionen*). Cohn, B., *Med. Klin.* 24: 1863. 1928.

The results of the treatment of ovarian deficiency with intravenous injections of an ovarian extract are briefly reported. A series of fifty patients ranging in age from puberty to the menopause having symptoms which were thought to be due to an ovarian deficiency were followed over a period of three years. The extract used was an albumen free, water extract of whole ovary. From one to five cc. were given at one dose. As a rule twelve injections were necessary to relieve the symptoms. Those patients who did not respond to the treatment were considered neurasthenics instead of having a true deficiency of the internal secretion of the ovary. Similar results were obtained with the diathermy when using the positive electrode in the vagina. No case reports were given.—Merrill Smeltzer.

The duration of corpus luteum activity in pregnancy (*Sur la durée de l'activité lutéinique pendant la gestation*). Courrier, R. and R. Kehl, *Compt. rend. Soc. de biol.* 101: 345. 1929.

Pregnant rabbits in which all of the young were in one horn of the uterus were chosen and the changes in the uterine wall of the free horn were followed. These changes were similar to those following infertile mating when effects of the corpus luteum disappear after twenty-four days. In the pregnant animal, the return of the uterine wall to normal was somewhat slower but all evidence of corpus luteum influence disappeared some time before the close of pregnancy.—J. C. D.

The heterogeneous testis transplant problem as applied to white rats and mice. Crisler, G., *Am. J. Physiol.* 90: 623. 1929.

Palpable well-vascularized nodules showing the persistence of tubules for five to six months resulted, in 43 experiments, from mouse testes transplanted into rats. By the criteria of the French workers about 79 per cent of these grafts were viable and functional, but by the author's criteria they had simply persisted anatomically and were degenerating.—R. G. H.

Ovarian responses. Differences elicited by treatment with urine from pregnant women and by freshly implanted anterior lobe. Engle, E. T., *J. A. M. A.* 93: 276. 1929.

Previous work has shown that the daily transplantation of anterior lobe into immature female mice results in a marked follicular growth followed by ovulation. Treatment of immature female mice with the urine of pregnancy results in follicular growth, with atresia of follicle and ovum, and effective prevention of ovulation by the transformation of the follicle into a corpus luteum with retained ovum. It is difficult to consider the two types of response as being due to the same factor from the anterior lobe.—Author's Summary.



**Mechanism of ovulation in the rabbit. II. Ovulation produced by the injection of urine from pregnant women.** Friedman, M. E., *Am. J. Physiol.* 90: 617. 1929.

It was found to be impossible to produce ovulation in the rabbit by the transplantation of as many as fifteen fresh rat hypophyses, or by the intraperitoneal injection of twenty-four rat hypophyses. Intraperitoneal injection of urine from pregnant women produced luteinization of the resulting corpora hemorrhagica in the rabbit ovary. A single intravenous injection of urine from pregnant women provoked ovulation in the rabbit. The samples of urine so far obtained from non-pregnant women have been utterly without effect on the rabbit ovary, either when injected intraperitoneally or when injected intravenously.—Author's Summary.

**A case of hypogenitalism (Über einen Fall von Hypogenitalismus).** Galant, J., *Virchow's Arch. f. path. Anat.* 267: 648. 1928.

The main features of hypogenitalism are: cutis marmorata, akrocyranosis, and underdeveloped genitalia. In a female patient of 23 years, the author found cutis marmorata, cyanosis of hands and feet, hypotrichosis, underdevelopment of the genitalia, and eunuchoid collections of fat. The patient began menstruating at 19 years and had been pregnant. These in all suggest the presence of a constitutional anomaly. Eunuchoidism was ruled out because of a successful pregnancy while infantilism was eliminated because of the adult mentality of the patient. He concludes that this is a case of hypogenitalism due to hypopituitarism. The literature is surveyed to a limited extent and various differential diagnoses are discussed.—Wm. Susman.

**Note on folliculine in the urine of cancerous patients (Recherche de la folliculine dans les urines des cancéreux).** Harde, E., P. Henri and J. Batier, *Compt. rend. Soc. de biol.* 100: 491. 1929.

In patients with cancer, as in pregnant women, tissue is growing rapidly. In certain cases folliculine could be demonstrated in urine from both men and women with cancer, when the production of oestrous changes in the vagina of mice was used as a test.

**New experiments with transplantation of desiccated ovaries (Weitere Untersuchungen über die Überpflanzung getrockneter Eierstöcke).** Kallas, H., *Virchow's Arch. f. path. Anat.* 273: 524. 1929.

The question of transplantation of desiccated ovaries was examined. The results were identical with those communicated by Lipschütz. There were 8 successful cases in which the ovary suffered a loss of up to 50 per cent of weight. Similar grafts were in full endocrine function about 5 months later. The differential survival at different degrees of desiccation (per cent of loss of weight) also has been studied. Together with the nine successful experiments of Lipschütz the total number of successful cases after a loss of 60 per cent by desiccation was seventeen out of thirty. There was no positive case in a group of 11 animals in which desiccation was more than 60 per cent.

—A. Lipschütz.

**Corpus luteum and glandular phase of the mammary gland in the rabbit (Corps jaune et phase glandulaire mammaire chez le lapin).** Kallas, H. and L. Lipschütz. *Compt. rend. Soc. de biol.* 100: 981. 1929.

**Hyperfeminization in the rabbit (Über Hyperfeminierung bei Kaninchen).** Bull. d'histologie appliq. à la physiol. 6: 273. 1929.

Ovaries have been engrafted into castrated male rabbits. There was in two cases a hypertrophy of the mammary gland or hyperfeminization as formerly observed by Steinach and others in the guinea pig. The mammary gland revealed a development similar to that in pseudopregnancy as observed by Ancel and Bouin in the female rabbit under the influence of the corpus luteum. Now, the ovarian graft in the male rabbit behaved like that in the male guinea pig, i. e., there were no corpora lutea and only distended follicles. From these experiments it is concluded that mammary development, characteristic of pregnancy and pseudopregnancy, can take place during the follicular phase.

—A. Lipschütz.

The Ganglion cervicalia uteri and the oestrous hormone. Kennedy, W. P., Edinburg M. J. 36: 75. 1929. (Transactions of the Edinburgh Obstetrical Society.)

In spayed mice this ganglion shows regressive changes, which involve the chromaffin cells and nerve cells. Injections with follicular extract and certain vegetable derivatives having a similar effect restore the ganglion to its normal appearance.—J. C. D.

Organ extracts as uterine stimulants (Organertraktgemische als Wehenmittel). Kohler, R. and H. Porges, Zentralbl. f. Gyn. 51: 3042. 1927.

Women in the first stage of labor with varying degrees of uterine inertia were studied to determine if thymus extract has a specific effect on pituitrin which makes the combination of the two safe to be used in the first stage of labor. Extracts other than that of the thymus were used with pituitrin. Cases were briefly summarized in which organic extracts of placenta, ovary and breasts combined with pituitrin were used. No difference was noted in the effects of the various combinations. From these studies it was concluded that thymus extract has no effect on the action of pituitrin. Tetanic contraction of the uterus does occur with thymophysin and two such cases are reported. Such contraction depends on the concentration of the uterine activating substance in the body.—M. Smeltzer.

The actual acidity in single sections of the male gonadal apparatus of rats and its hormonal significance (Die reelle Acidität in den einzelnen Abschnitten des männlichen Genitalapparates der Ratte und ihre hormonale Bedingtheit). von Lanz, T., Arch. f. d. ges. Physiol. 222: 181. 1929.

Using a hollow-needle, gold-iridium electrode, the true acidity was determined with pure hydrogen and mixtures of hydrogen and carbon dioxide, with surviving organs of normal animals, with young animals with ligatured ducts efferentes, and with one-sided and completely castrated animals. Testicular fluid has a pH of 7.19-7.37, that of the epididymis 6.48 to 6.61, while that of the prostate secretion is about 7.14. The secretion of the seminal vesicles has a pH of 6.32 to 6.34. The first and third are slightly, the second and fourth strongly buffered. The pH value is independent of spermatogenesis. Total castration influences it, the values changing to that of the blood. The internal secretion of the testis is active after ligation of the ducts efferentes.—A. T. C.

The occurrence of female sexual hormone (Menformon) in the urine of men (Über das Vorkommen weiblichen Sexualhormons (Menformon) im Harn von Männern). Laqueur, E., E. Dingemans, P. C. Hart and S. E. de Jongh, Klin. Wchnschr. 6: 1859. 1927. Abst., Biol. Absts. 3: 591.

As much as 50 mouse units of female sexual hormone has been isolated from a liter of urine from men. The product has been purified so that 1 unit is contained in 0.3 mgm. of dry product.

Transplantation of conserved ovaries. II. Endocrine action of ovaries preserved at room temperature (Transplantation von konserviertem Ovarium. II. Endokrine Wirkung von bei Zimmertemperatur konservierten Ovarien). Lipschütz, A., Arch. f. d. ges. Physiol. 220: 29. 1928.

Such ovaries are active after preservation for from 1 to 8 days at a temperature of 14-20 degrees C. Transplanted to male guinea-pigs they produce hyperfeminization. Such preservation at room temperature appears to damage them to a greater extent than when preserved on ice.—A. T. C.

Transplantation of the desiccated ovary (Transplantation von getrocknetem Ovarium). Lipschütz, A., Virchow's Arch. f. path. Anat. 272: 245. 1929.

It was shown formerly by the writer that the ovary of the guinea-pig can be successfully grafted even after having been kept outside the body on ice or at room temperature for more than two weeks. The experiment was tried of grafting ovaries of the guinea-pig which had undergone considerable loss of water. If desiccation by exposure to  $\text{CaCl}_2$  is complete the ovary never took. On the contrary, a take was possible if the loss of water was an incomplete one.

Of 21 experiments 9 were successful, with ovaries which suffered a loss of weight averaging 30 to 55 per cent. These ovaries can survive and function in the host during several months as corroborated by the histological examination of the graft 5 months after transplantation. There is no question about the action of the hormones already present in the ovary before engrafting; the experiment is successful with infantile ovaries which never before produced oestrus. Though positive results can be obtained with desiccated ovaries the experiment reveals the fact that loss of water is very detrimental to the organ. The number of successful cases when fresh, normal ovaries were used was about 85 per cent. When partly desiccated ovaries were used the number of successful cases was much less. There were also a considerable number of cases in which the graft had taken and functioned but became absorbed later on. The time of latency with partly desiccated ovaries is also lengthened. The microscopical examination of the desiccated ovary before transplantation reveals the fact that the primary follicles suffer retraction under the influence of the loss of water.—Author's Abst.

Relations between the quantity and the action of female sexual hormone (Beziehungen zwischen Menge und Wirkung des weiblichen Sexualhormons). Lipschütz, A., *Biochem. Ztschr.* **215**: 222. 1929.

The principles of the biological assay of the follicular hormone are discussed, comparing less purified extracts from the urine with highly purified ones. Less purified extracts produce when 100 or 200 units have been injected, a cornified stage of 1 to 2 weeks' duration; the same number of units of a highly purified extract (about 1 to 3/1000 mgm.) produces a cornified stage of only about 2 days. The number of injections is very important with highly purified extracts; if one takes as a unit the quantity which when distributed in 6 injections during 60 hours produces the cornified stage in the majority of the animals of the group, then a hundred units given in one injection will produce a lower percentage number of cases with oestrus than one unit. The reaction of the mouse to the follicular hormone is not influenced by diuresis; 1 cc. of water, of Ringer solution or of Ringer of double concentration can be given daily for several days without influencing the duration of the cornified stage after injection of great quantities of hormone. The all-or-nothing law as applied to the follicular hormone is also discussed. It is shown that the law is in accordance with all experimental data available. Oestrus is evidently produced when a certain concentration of hormone persists for a certain time. The incomplete reaction can be explained, assuming that in these cases the threshold concentration did not persist long enough. The necessity of establishing international rules for the biological assay of the follicular hormone is insisted upon.—Author's Abst.

Oxygen use of the isolated ovary of the mammal (Über den Sauerstoffverbrauch des isolierten Säugetierovariums). Lipschütz, A., *Arch. f. d. ges. Physiol.* **223**: 56. 1929.

New observations on the metabolism of the isolated ovary (Nouvelles observations sur le métabolisme de l'ovaire isolé). *Compt. rend Soc. de biol.* **100**: 982. 1929.

The oxygen consumption of the isolated ovary of the guinea-pig was studied under different experimental conditions. There is an oxygen use for several days at temperatures lower than 38 degrees C., even on ice. The difference between oxygen use at various temperatures is  $Q_{10}=2, 5$ , in such a manner that oxygen use on ice was about 20 to 40 times less than at body temperature. Oxygen use per mgm. of ovary of the guinea-pig is about one-third as much as in the mouse. The law of "liminal thickness" of Warburg has to be taken into consideration when the maximal oxygen use of the ovary is examined. The better results with transplantation of isolated ovaries when kept on ice can be explained on the assumption that oxygen use being highly reduced at low temperatures the thickness of the ovary is not greater than the liminal thickness at this low temperature. If the isolated ovary has been kept at temperatures lower than 0°, there is an oxygen use when examined afterwards at about 18°, but it diminishes rapidly during 24 hours; at body temperature such an ovary shows oxygen use only for a short time. The same phenomenon is seen in triturated ovaries. Freezing of the ovary is thus identical with mechanical destruction of the organ.—A. Lipschütz.

Castration in the pigeon (Castration chez le Pigeon). Lipschütz, A. and O. Wilhelm, *J. de physiol. et de path. gén.* 27: 1. 1929.

The plumage of the male pigeon is not influenced by castration when observed during more than 14 months. Sexual behavior seems to be influenced. A testicular fragment, if not too small, is able to protect against loss of sexual behavior. Absence of sexual demorphism in the plumage of birds can be evidently caused in two different ways: (1) the feather germ is influenced by ovarian and testicular hormones (Sebright type; Morgan Roxas); (2) the feather germ is influenced neither by ovarian nor by testicular hormones (Columba type).—A. Lipschütz.

Note on the properties of urine from pregnant women (Contribution a l'étude des propriétés de l'urine de femme gravide). Orban, F. and M. Watrin, *Compt. rend. Soc. de biol.* 100: 435. 1929.

Interpretation of the changes induced in the ovaries of young mice by urine from pregnant women (Sur l'interprétation des phénomènes provoqués dans l'ovaire impubère de souris par l'injection d'urine de femme gravide). Orban, F. and M. Watrin, *Compt. rend. Soc. de biol.* 100: 438. 1900.

Urine from pregnant women has a specific effect peculiar to itself on the ovaries of mice before puberty. This effect is not that of the "prehypophysine," but is characterized by intense congestion of the ovary with rupture of the capillaries; an exaggeration of normal degenerative changes. The vaginal changes in mice under these conditions are not a safe guide to the ovarian.  
—J. C. D.

Can senescence be retarded (La vecchiaia può essere ritardata)? Pende, N., *Scientia*, 42: 11. 1927. *Abst., Biol. Absts.* 3: 593.

The endocrine mechanism operates throughout the life of the individual in a series of normal changes, which may be modified by heredity, function, and interaction of different endocrine glands. If the whole process is clearly apprehended, it may lead to such use of endocrine therapy as to ward off premature senility.

"Progynon"—Schering—A new cyclus hormone preparation ("Progynon"—Schering, ein neues Zyklus-Hormonpräparat; Amenorrhoe [ohne und mit Hypoplasia Genitalis]). Streck, A., *Klin. Wchnschr.* 7: 1172. 1928.

Progynon is an aqueous solution of the placenta of the cow, prepared commercially in the form of suppositories or pills. It has the property of stimulating estrus. It has been standardized by the Allen, Doisy rat unit biological test and tested clinically by use of the Aschheim Zondek technique of recovering the hormone in the urine. The authors used animals and women to test the toxic effects and found no local, general, protein or toxic results even after enormous doses, given orally or rectally. The study revealed that an initial dose of 250 rat units or 500 rat units was required, repeated every day or every other day and that the summation of dosage necessary to produce menstruation was 500 to 4,500 units given in from two to eighteen doses, and that treatment took from one to five weeks. The results were better and more lasting the oftener the menses had occurred before treatment and the less marked the genital hypoplasia. The author also considers the causes of hypoplasia genitalis, and gives the result of a study of twenty-six cases of amenorrhea with or without hypoplasia genitalis. Six typical case histories are cited. The use of progynon is indicated in cases with ovarian hypofunction and genital hypoplasia, and contraindicated in cases with hypogonadism where there is a general disease or inflammation of the genital organs. In conclusion the author emphasizes the value of oral and ambulatory treatment, the use of large initial doses and a summation of 500 to 4,500 rat units required, and that the results are those of substitution. The best clinical criterion of the value of the product is the recurrence of menstruation.—F. Firestone.

Eczema and ovarian disturbances (Ekzem und Ovarialstörungen). Szego, P., *Zentralbl. f. Gynäk.* 52: 1593. 1928.

This is a report of the results of glandular therapy in 16 cases of dermatitis and eczemas associated with disturbances of ovarian function. Little

therapeutic effect was noted on skin diseases associated with hypermenorrhea, whereas good results were obtained when the skin disease was associated with oligomenorrhea or amenorrhea, even in pregnancy and the climacteric. Other systemic conditions were not excluded. In the treatment of the reported cases "glanduovin" was used intravenously and intramuscularly on alternate days. The dosage varied from 2 to 5 cc., a total of about 60 cc. being given in a course of 16 injections. With this treatment the itching of the external genitalia disappeared and normal menstruation was re-established.—M. R. White.

Experiments with extraction of the female sexual hormone from the urine of the pregnant woman (*Über Versuche zur Gewinnung des weiblichen Sexualhormons aus dem Harn der Schwangeren*). Veshnjakov, S. and A. Lipschütz, *Biochem. Ztschr.* 210: 348. 1929.

A description is given of a simple method of extraction of follicular hormone from the urine of pregnant women following the manner of Zondek and Aschheim. One liter of alcohol is added to 10 liters of urine; the alcohol is evaporated and the residue is extracted with ether; the extraction is repeated several times. After evaporation of the ether the residue is treated with 10 per cent NaOH. Extraction with ether is again repeated several times. Repeated extraction with ether and water gives a prunty of about 1/1000 mgm. per M. U.—A. Lipschütz.

The hormone of heart movement. XI. Further experiments with the heart-hormone preparation (*Ueber ein Hormon der Herzbewegung. XI. Weitere Froschherzversuche mit dem Herzhormon präparat*). Haberlandt, L., *Arch. f. d. ges. Physiol.* 221: 576. 1929.

Extracts completely free from histamine give the effects previously described by the author.—A. T. C.

Further experiments on the heart hormone. The active principle of Haberlandt's frog-heart hormone (*Fortgesetzte Untersuchungen über das Herz-hormon. Der wirksame Bestandteil des Haberlandtschen Froschherzhormons*). Rigler, R., *Arch. f. d. ges. Physiol.* 221: 509. 1929.

The action attributed by Haberlandt to an internal secretion is due to the combined effect of potassium ions and certain alcohol-ether soluble compounds (described by A. J. Clark and by Loewi) with a positive inotropic effect.

—A. T. C.

Hypophyseal cachexia (*Über einen Fall von hypophysarea Kachexie*). Altmann, F., *Frankfurt Ztschr. f. Path.* 36: 393. 1928.

In a woman of 48 cachexia, loss of hair, dry skin, fine tremors, atrophy of genitalia, lead to a diagnosis of hypophyseal cachexia. At death the complete clinical diagnosis was caseous pneumonia, epilepsy, severe anaemia, and pluriglandular endocrine insufficiency. At autopsy there was found a large pineal body, extreme atrophy of the hypophysis, caseous pneumonia of the left lung, extreme atrophy of the thyroid, large kidneys and small adrenals rich in lipoids. Microscopic examination showed the pars glandularis of the hypophysis represented by only a few cells and no evidence of inflammation. The thyroid parenchyma was degenerate as well as atrophic. The adrenal medulla was much reduced in size. In the kidneys there were fatty degeneration of the tubules and arteriosclerosis. In all the essential feature is a disease of the endocrines with the primary lesion in the pituitary. That the tubercular process is the primary cause of endocrine lesions can not be substantiated. The more likely cause is some constitutional and endogenous factor as in pre-senile involution—Wm. Susman.

Laurence-Biedl disease (*Ein Beitrag zur Laurence-Biedlschen Krankheit*). Bernhardt, H., *Ztschr. f. klin. Med.* 107: 488. 1928.

Laurence-Biedl disease includes Frohlich's syndrome together with retinitis pigmentosa, optic atrophy and polydactylia and psychical disturbances. In all there are 20 recorded cases. Two further cases are here described, with complete histories. Two brothers 16½ and 10¾ years of age showed dystrophia adiposo-genitalis, polydactylia, mental underdevelopment and enlarge-

ment of the sella turcica. The younger had diabetes insipidus also. Numerous metabolic and biochemical tests were made and the results discussed. In treatment, thyroidin and calcium were beneficial. The author concludes that the optic atrophy, polydactylia and the mental underdevelopment point to a congenital origin but that the dystrophia adiposo genitalis is due probably to a disturbance of the hypophysis and mid brain.—Wm. Susman.

Report of several cases of diabetes insipidus treated with powdered posterior lobe by nasal administration (Quelques cas de diabète insipide traités par la poudre hypophysaire [lobe postérieur] administrés par voie nasale). Choay, A. and L. Choay, *Rev. franç. d'endocrinol.* 6: 423. 1928.

Nasal applications of powdered gland give results similar to hypodermic injections, but more gland, by weight, is required to produce equivalent results. There seems to be no more danger in this method than in the hypodermic, and it is considered more convenient.—B. C.

Precocity from hypopituitarism. Elias, L. W., *South. M. J.* 22: 595. 1929.

The author reports two cases of sexual precocity in girls, which he thinks is due to hypopituitarism. The first case is that of a 3-year-old girl who weighed 6½ pounds at birth, 45 at 9 months and now weighs 114 pounds. She has a vaginal discharge which has continued at intervals of from six to eight weeks for the past year. It is yellowish or slightly pink at times. The second case is a colored girl of 9 years who has the appearance of one of 13 years. She is mentally backward. There is a heavy growth of pubic and axillary hair which has been present for the past two years. The breasts are well developed. The clitoris is not enlarged. There is no history of precocious menstruation in her family. Menstruation began at the age of two years and has been regular every four weeks ever since, lasting about three days at a time. The character of the flow is normal.—M. B. G.

Anterior pituitary hormone in blood during pregnancy. Fluhmann, C. F., *J. A. M. A.* 92: 1744. 1929. *Abst., A. M. A.*

A study was made to obtain some information regarding the presence of hormones, and particularly the anterior pituitary hormone in the blood of pregnant women, and to note the changes set up in the genital organs of immature female white mice following the injection of human blood serum. The reactions found in the genital organs of immature white mice following the injection of blood serum from pregnant and nonpregnant patients may be classified in three groups, those attributed to the effects of a hormone from the anterior pituitary gland being considered the most important. One hundred patients were examined. Forty-eight represented normal pregnancies, and of these two gave negative results, 11 showed the presence of ovarian hormone alone, and 35 were positive for anterior pituitary substance. Of 52 controls, two patients showed ovarian hormone, and six anterior pituitary hormone. Of the latter, four were patients with either an operative or a radiation castration, and two had a functional amenorrhea.

Mechanism of the influence of pituitary extracts on blood sugar (Beiträge zum Mechanismus der Blutzuckerbeeinflussung durch Hypophysenextrakte). Fritz, G., *Arch. f. d. ges. Physiol.* 220: 101. 1928.

Intramuscular injection of posterior pituitary extract into mammals increases the blood sugar. The action is secondary to adrenine mobilization, for it is not produced in adrenalectomized animals. The adrenine mobilization is a result of general stimulation of the sympathetics.—A. T. C.

Case of pituitary tumor treated by X-rays. Griffith, A. D., *Proc. Roy. Soc. Med. Sect. Ophthalm.* 22: 31. 1929.

In a case of pituitary tumor occurring in a male of 48, the headache, giddiness, and staggering were accompanied by difficulty in reading. Examination revealed central bi-temporal scotomata. Twenty-six X-ray treatments of the pituitary resulted in a disappearance of headache and giddiness, a gradual improvement of the fields of vision and finally the ability to read normally.

—I. B.

Function of the hypophysis and region of the tuber cinereum and infundibulum in the toad (Les fonctions de l'hypophyse et de la région infundibulo-tubérienne chez le Crapaud). Houssay, B. A. and L. Giusti.

The hypophysis and the testis in the toad *Bufo Marinus* (L.) Schneid (L'hypophyse et le testicule chez le Crapaud *Bufo marinus* [L.] Schneid). Houssay, B. A. and J. M. Lascano-Gonzales, *Compt. rend. Soc. de Biol.* 101: 935, 938. 1929.

Numerous and carefully controlled experiments involving extirpation of the hypophysis and deliberate injuries to the infundibular region brought out first a hyperactivity of the gland, marked by a darkening of the skin at the moment of operation and then pallor, testicular atrophy, asthenia, and convulsions with a corresponding rise in mortality. Pallor is a specific symptom dependent on loss of the pars intermedia. The other symptoms are seen less frequently where the anterior lobe alone is removed. The formation of a cutaneous pellicle, discharge of immature ova, and polyuria are seen in total hypophyseal removal but especially in cases of infundibular damage. The symptoms of hypophyseal extirpation can be prevented by frequent transplants of toad pituitary.—J. C. D.

The anti-diuretic action of separated principles of the posterior lobe of the pituitary body. Hemingway, A. and J. M. Peterson, *J. Physiol.* 67: 24. 1929.

Perfusion of heart-lung-kidney preparations with blood to which was added vasopressin and oxytocin, shows that both have prolonged anti-diuretic effects, that of vasopressin being the more powerful. This substance also increases the resistance of the kidney capillaries and diminishes the renal blood flow. There is an accompanying increased chloride concentration and an increased total output of chloride.—C. J. R.

Acromegaly with reference to eye and ear findings. Hertz, W. J., *Atlantic M. J.* 32: 768. 1929.

This is a report of a case of acromegaly of more than 8 years' duration occurring in a white woman of 28. In July, 1928, the patient complained of earache. Examination showed a bulging tympanic membrane which was incised, with relief of symptoms. A few weeks later ear discomfort returned. Because of a previous history of diabetes a diabetic regime was outlined. The patient was admitted to the hospital where it was discovered that the blood sugar was 440 mgm. per 100 cc. and the Wassermann reaction was 4 plus. Urinalysis revealed a trace of albumin and 2.2% sugar, although it was negative for acetone, diacetic acid and casts. Insulin and anti-diuretic medication was now given. On September 6th the right mastoid antrum was opened and a large abscess evacuated. On the fourth day after operation the temperature rose to 101.2 and patient complained of dizziness. At this time spontaneous nystagmus toward the affected side was observed. This, however, disappeared and the temperature became normal in 48 hours after removal of the iodoform gauze packing in the wound. The patient then developed an acute mania with a septic type of temperature and died on the ninth day after operation. A postmortem was not permitted.—I. B.

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Antagonism between the hypophysis and insulin in the toad (Antagonisme entre l'hypophyse et l'insuline chez le Crapaud). Houssay, B. A. and Dora Potick, *Compt. rend. Soc. de Biol.* 101: 940. 1929.

The authors demonstrated that posterior lobe extract injected twenty-four hours after an injection of insulin reduced the inhibitory power of the former without interfering with its oliguric action. The melanophores were over expanded. Removal of the hypophysis makes the toad very susceptible to the toxic effects of insulin. Removal of the glandular lobe has somewhat less effect and cauterization of the infundibular region has no influence. Extracts of bovine anterior and posterior lobes protect against this toxic action in hypophysectomized toads. Daily grafts of toad anterior lobe protects against insulin toxemia while posterior lobe implants are ineffective.—J. C. D.

Treatment of constitutional obesity with hypophyseal preparations. Hunt, T. C., *Wien. klin. Wchnschr.* 41: 1682. 1928.

Hunt reviews the literature bearing on the effect of posterior lobe extract on fat metabolism. It has been accepted that pituitrin causes mobilization of fat, increasing the store in the liver where it is evidently metabolized. According to Raab, during the state of fasting in dogs, it reduces the amount of fat in the blood. Hunt undertook some experimental studies in four patients suffering with constitutional obesity, in which he used various extracts of the posterior lobe administered subcutaneously. The injections were given daily and varied in number from 6 to 13. He failed to get any reduction in weight. This is contrary to the results obtained by Langdon Brown, who reported a case in which there occurred a marked reduction in weight following injections of pituitrin. Hunt concludes that his experiments do not justify the use of posterior lobe preparations to produce loss in weight.—H. G. Beck.

The action of extract of pituitary on the blood sugar after pancreatectomy. Imrie, C. G. J., *J. Physiol.* 67: 264. 1929.

In dogs, after pancreatectomy, if insulin is withheld 44 hours or less, a rise in blood sugar results from pituitary extract as in intact animals. After 70 hours without insulin, this rise does not occur. Under the latter conditions adrenalin also fails to increase blood sugar. Muscle glycogen is not affected, therefore the hyperglucemia is due to hydrolysis of liver glycogen. —C. J. R.

Precocious sexual maturity induced by parabiosis (*Puberté précoce par parabiose*). Kallas, H., *Compt. rend. Soc. de biol.* 100: 979. 1929. Parabiosis and anterior lobe of the hypophysis (*Parabiose und Hypophysenvorderlappen*). *Arch. f. d. ges. physiol.* 223: 232. 1929.

When two infantile rats weighing about 15 grams each, one castrated, the other not castrated, are parabiotically united, a precocious sexual maturity is established in about 7 days in the uncastrated animal. The vaginal mucosa is keratinized, the uterus undergoes the characteristic changes of oestrus. Oestrus can persist 6 days without interruption. There is follicular ripening in the infantile ovary under the influence of the castrated parabiotic partner. At the end of the second week corpora lutea are produced and oestrus is interrupted. Since these phenomena are identical with those observed after hypophyseal injections into an infantile animal, it is concluded that the changes as observed in the genital region in parabiosis are to be explained by hypophyseal substances passing from the castrated animal to the uncastrated one. This is corroborated by the experimental fact that production of sexual maturity in the uncastrated partner can be hastened by hypophyseal injections into the castrated one. Passing of hypophyseal substances from the castrated partner into the uncastrated one begins a few days after establishing the parabiosis. Since sexual maturity is produced by parabiotic union with an infantile castrate it is concluded that the hypophysis of the infantile animal is able to produce and to secrete the X-substances in question. The fact that sexual maturity in the uncastrated partner is produced only if the ovaries of the castrated partner have been removed, indicates that the infantile ovary acts in some way on the hypophysis.—A. Lipschütz.

Law of follicular constancy, law of puberty and anterior lobe of the hypophysis (*Ley de la constancia numerica folicilar, ley de la pubertad y lobulo anterior de la hipofisis*). Lipschütz, A., *Boi. de la Soc. de Biol. de Conc.* 2: 3. 1929.

The qualities of the hypothetical X-substances postulated from the facts expressed in the law of follicular constancy and the law of puberty, and the properties of the hypophyseal substances are identical; both are similar in male and female, both are produced in the normal and in the castrated animal, both are used in the glands as supposed by Sand. Since there is a complete parallelism between both sets of experimental data, the author believes that the hypophysis is responsible for the production of the X-substances.

—Author's Abst.



**Hypophysis and law of puberty (Hypophyse und Gesetz der Pubertät).** Lipschütz, A., H. Kallas and R. Paez, Arch. f. d. ges. Physiol. 221: 6. 1929.

The hypophyses of male and female guinea-pigs were able to produce sexual precocity in infantile female mice even when the donor had been castrated for more than a year. The hypophysis was active when taken from a male guinea-pig hyperfeminized by ovarian transplantation. There was a precocious follicular development but no formation of corpora lutea. A single hypophysis of a new-born guinea-pig usually produced sexual precocity in the infantile mouse. The experiments of Smith and Engle with the infantile hypophysis of the rat are corroborated by the above experiments. The hypophysis of an old dog (14 years) was also active in producing precocious development in the infantile female mouse.—A. Lipschütz.

**The pituitary and the law of puberty (Hypophyse und Gesetz der Pubertät).** Lipschütz, A., H. Kallas and R. Paez, Arch. f. d. ges. Physiol. 221: 695. 1929.

The anterior pituitary of castrated male and female guinea-pigs acts in the same way on the uterus of the infantile mouse as does the normal pituitary, even when castration had been performed more than a year previously. The pituitary of hyperfeminized guinea-pigs is similarly active, as is also that of the young rat, and the young guinea-pig of either sex. Similar effect on the uterus was obtained by injection of the pituitary of a senile dog. Smith and Engle's conclusion that the anterior pituitary of the infantile animal already produces its secretion and that of the aged animal still produces it is confirmed.

—A. T. C.

**Epilepsy in children.** McQuarrie, I., Am. J. Dis. Child. 38: 451. 1929.

There seems to be a tendency for epileptic subjects to retain water during the active stage of the disease in amounts which are harmful. Convulsions tend to increase when there is a positive water balance while diuresis favors the prevention of further seizures. Parenteral administration of the solution of pituitary or of the antidiuretic hormone of the hypophysis causes the development of a positive water balance and the occurrence of seizures.—M. B. G.

**The antidiuretic effect of solution of pituitary dropped intranasally in a case of diabetes insipidus.** Mettel, H. B., Am. J. Dis. Child. 38: 342. 1929.

A case of diabetes insipidus in a girl 9 years of age is reported, with all the physical and laboratory findings. Charts are given showing the effect on the urinary output of the administration of pituitary extract subcutaneously and intranasally. Equal effects were obtained by each method. There was a marked increase in weight of the patient. It is concluded that the intranasal application of posterior pituitary solutions is as efficacious as other methods heretofore described. Attention is drawn to the unusual gain in weight, and comments are made concerning the relation of this result to the function of the pituitary gland.—Author's Abst.

**Specific dynamic action and the pituitary. (Rat experiments.) (Ueber spezifisch-dynamische Wirkung und Hypophyse [Rattenversuche]).** Nothhaas, R., Arch. f. d. ges. Physiol. 221: 763. 1929.

Feeding anterior pituitary substance to rats caused a slight increase in the specific dynamic action.—A. T. C.

**The effect of anterior lobe hormone on gaseous metabolism in rabbits (Über den Einfluss des Vorderlappenhormons auf den Gaswechsel beim Kaninchen).** Reiss, M. and K. A. Winter, Endokrinol. 3: 174. 1929.

The authors injected into rabbits and dogs extract of anterior lobe pituitary or preparation of the sex-stimulating pituitary product obtained from urine by Biedl's method. They obtained marked stimulation of the vagina and breasts and, in 2 dogs, milk production. The maturation of true corpora lutea was hastened. The blood cholesterolin was increased in normal but not in ovariectomized animals. Clean-cut evidence of an influence of pituitrin on blood cholesterolin was not obtained.—R. G. H.

Congenital and familial disease characterized by an adiposogenital dystrophy (Maladie congénitale et familiale caractérisée par une dystrophie adiposogénitale associée à une rétinite pigmentaire et une polydactylie). Ricaldoni, A. and A. Isola, Arch. de méd. d. enf. 32: 27. 1929.

The authors reported four cases, brothers and sisters who were the only survivors of a family of eight children. The four children were afflicted with the same malady, and exhibited obesity of the hypophyseal type with sexual hypoplasia, retinitis pigmentosa, polydactylism, and psychic abnormalities. Visual disturbances consisted of diminution of vision, which appeared in all the children at an early age, hemianopsia, and contraction of the visual field. Nystagmus was also mentioned. Polydactylism occurred in all of the children in the form of supernumerary fingers or toes. These were always inserted on the outer side of the metacarpal or metatarsal joints. All four children were timid, very emotional and mentally deficient. Laboratory examinations were essentially negative except roentgenograms of the skull, which showed small sella turcica with elongation of the clinoid processes. There was no delay of epiphyseal union. Both parents were normally developed and healthy. Reference is made to the report of similar cases by Bardet, Farnes, Biedl, and others. No satisfactory explanation is offered as the cause of the disease. The authors stress the familial character of the malady.—H. G. Beck.

Classification of the hypophysis syndromes (Essai de classification des syndromes hypophyso-tubériens). Richard, G., Rev. franç. d'endocrinol. 7: 224. 1929.

After examining the several methods of classifying the syndromes of pituitary origin, a new classification is proposed, namely, (1) systemic symptoms including (a) abnormal osteology and (b) nutritive disturbances, (2) non-systemic such as migraine and epilepsy, (3) pluriglandular symptoms.—B. C.

Hormonal activity of anterior lobe of hypophysis of fetus (Untersuchungen über die hormonale Wirksamkeit des Hypophysenvorderlappens des Fötus im Tierversuch). Schultze-Rhonhof, F. and R. Niedenthal, Zentralbl. f. Gynäk. 53: 902. 1929.

Anterior lobes of the hypophyses of fetuses were tested for the hormone which influences the ovary. The test animals were 6 to 8 gram mice. Subcutaneous implants were made after the method described by Smith and Engle and by Zondek and Aschheim. Three human fetuses of 30, 35 and 41 cm. and several fetuses of cattle were used as sources of anterior lobes. Stimulation of growth of follicles occurred in many cases with oestrous growth in the vagina and uterus. Although in some cases ovarian stimulation did not induce ovulation, enough growth resulted to justify the conclusion that the anterior lobe of the hypophysis of the fetus has already begun secretion of the hormone which influences the ovaries.—E. A.

Water intoxication in cases of diabetes insipidus. Snell, A. M., M. Clin. North America, 12: 1667. 1929.

A valuable paper on postencephalitic diabetes insipidus with three case histories. This form of diabetes insipidus differs from that due to other lesions in the variability of intake and output and in response to pituitrin. In certain cases a compulsion thirst may exist which may amount also to a mania for water; this thirst when existing in patients with defective judgment may lead to the consumption of enormous quantities of fluid. If their fluid intake is unrestricted or if the output of urine is reduced by pituitrin, there may be episodes undistinguishable from experimental water intoxication in animals.—I. B.

Experimental diabetes insipidus. Towne, E. B., Arch. Surg. 18: 1165. 1929. Abst., Arch. Neurol. & Psychiat. 22: 1055.

Towne attempted to produce diabetes insipidus in dogs by detaching the stalk of the pituitary gland. He found that the polyuria thus produced was transitory. He has searched through the literature and found that separation of the stalk rarely if ever produced permanent polyuria. From his experiments and from the literature he feels that the neurogenic theory of Camus and Roussy is not supported. He believes that these experiments strongly suggest

that diabetes insipidus is due to suppression of the secretion of the pars intermedia and the pars tuberalis.

**Insulin in acromegalic diseases.** Ulrich, H., Arch. Int. Med. 43: 785. 1929.

This article refutes the widely held opinion that insulin is as effective in hyperpituitary diabetes as it is in so-called pancreatic diabetes. The evidence upon which this opinion is based is analyzed, and most of it is shown to be fallacious. As a consequence, it is suggested that insulin be used for diagnostic purposes in cases of glycosuria that are suspected of having a hypophysial foundation. A demonstrable failure of insulin to produce its expected and usual results should be regarded as a link in the chain of evidence leading to a diagnosis of hyperpituitary disease.—Author's Abst.

**Action of posterior lobe extract on the tension of the cerebrospinal fluid (Action d'un extrait rétro-hypophysaire sur la tension rachidienne).** Urechia, C. I. and L. Dragomir, Compt. rend. Soc. de biol. 100: 384. 1929.

Subcutaneous injection of posterior lobe extract increases the pressure of the cerebrospinal fluid in about half an hour.—J. C. D.

**The action of insulin on the liver (Über die Einwirkung des Insulins auf die Leber).** Forsgren, E., Acta med. Scandinav. 70: 139. 1929.

It was found, in a control series of eight rabbits, that the glycogen content of the liver after about 5½ hours' fasting varied from 1.8 to 9.3 per cent. The histological findings presented corresponding variations, the lobules in what the author calls "the assimilatory stage of the functional cycle of the liver" containing much glycogen, and in "the secretory stage" very little. Nine rabbits were examined after about 5½ hours' fasting, in the course of which they had been given different amounts of insulin. The glycogen content showed variations similar to those in the control series, and the values showed no relation to the insulin dosage. The author suggests that insulin convulsions do not bring about a low glycogen content of the liver, but rather that the animals in "the secretory stage" are more susceptible to insulin intoxication. Insulin does not disturb the normal cycle of the liver function, nor does it promote the deposition of glycogen.—S. Wiking.

**A study of the blood pressure of patients with diabetes mellitus.** Adams, S. F., Am. J. M. Sc. 177: 195. 1929.

The blood pressures of 1001 diabetic patients in the Mayo Clinic were determined. The author chose an arbitrary standard of 150 mm. for systolic and 100 mm. for diastolic as indicating hypertension. The percentages in this series of cases were compared with blood pressure records of people who applied for insurance which were taken as normal for purposes of comparison. There was a greater percentage of hypertension among the diabetics than in the normals. The same, however, was true for hypotension. The author feels if hypertension is present, it is due to an associated abnormality and not to diabetes.—E. L.

**Hyperinsulinism.** Allan, F. N., Arch. Int. Med. 44: 65. 1929.

Hyperinsulinism due to overproduction of insulin from a tumor of the islands of the pancreas is now established as a disease entity. It is probable that hyperinsulinism may also be due to a functional disturbance of the pancreas. The differential diagnosis of hypoglycemia due to hyperinsulinism and hypoglycemia due to selective hepatic insufficiency is a difficult clinical problem. Two criteria may have value in differentiation; the effect of epinephrine hydrochloride and solution of pituitary, and the amount of sugar required to maintain the blood sugar level. When the hypoglycemic tendency is so strong that the patient is incapacitated, surgical treatment appears to promise relief. Three cases are described in which there was a constant tendency to severe hypoglycemia attributed to hyperinsulinism. In case 1, there was a carcinoma of the islands of Langerhans. In case 2, surgical exploration revealed a normal appearing pancreas. Resection of a part of the pancreas was followed by considerable relief. In case 3, in which medical treatment alone was given, the patient is still under observation.—Author's Summary.

Transplantation into a series of rats of two fragments of Jensen's sarcoma, one piece normal and one treated with insulin *in vivo*. Difference in development of these (Transplantation, a une série de Rats, de deux fragments de sarcome de Jensen, l'un normal, l'autre insulinisé *in vivo*. Différence de développement de ces tumeurs). Barral, P. and R. Cade, *Compt. rend. Soc. de biol.* 101: 1141. 1929.

White rats, carrying the sarcoma, were given 40 to 55 units of insulin in eight hours. These furnished the insulin treated grafts, while tumor-bearing rats without treatment furnished the control tumor grafts. Two grafts, one insulin treated and one control, were implanted into each experimental rat in symmetrical positions in the body. The grafts from the tumors in the insulin-treated rats invariably outgrew those from the controls.—J. C. D.

Histological research on islands of Langerhans in experimental scurvy (*Ricerche istologiche sulle isole di Langerhans nello scorbuto sperimentale*). Borghi, B., *Arch. Ist. Biochim. Ital.* 1: 69. 1929.

Guinea pigs on a scorbutic diet show the islands of Langerhans increased in size and mostly formed of chromophile cells. Guinea pigs on a "scorbutogenic" diet and injected with glucose showed a different result according to the epoch of the sugar treatment. With glucose injected at the beginning the islands looked smaller than the average, when the glucose was injected after a certain period of the "scorbutogenic" diet some hypertrophic islands were seen. The most of the island cells were chromophobe. The hyperplasia and hypertrophy of the insular tissue in the guinea pigs on a "scorbutogenic" diet are held as an effort to compensate the increased glycemia.—G. V.

Modifications in the secretion and motility of the stomach by the action of insulin and synthalin (*Modificaciones de la secrecion y motilidad gastrica por accion de la insulina y shitalina*). Bustamante, Garcia, *Arch. d'Endocrinol. y Nutricion*, 1: 295. 1928.

Insulin increases the secretion, motility and emptying time of the stomach though not in a constant manner. This leads some authors to believe that insulin acts on the parasympathetic nervous system. Synthalin, however, diminishes the gastric secretion but augments motility and emptying time. It is suggested that this property of insulin might be utilized in cases in which stimulation of acid secretion and gastric contractions are desired, as for example in asthenia with hypochlorhydria. In case of diabetics in whom, for special reasons, gastric accumulation is not desired, the concomitant use of atropin is suggested.—E. B.

The functional test of the pancreas (*Ueber die Funktionsprüfung des Inselorgans*). Depisch, F. and R. Hasenöhr, *Klin. Wchnschr.* 7: 1631. 1928.

The capillary blood-sugar curve shows the influence of insulin and its antagonists on the liver, but it is not able to give any certain data as to the absolute degree of action of the internal secretion of the pancreas. In following simultaneously the capillary and venous blood-sugar curve after a sugar test meal, it is possible to measure indirectly the intensity of insulin production by the difference between the glycemias. In normal individuals there exists usually a pronounced difference between them, while in diabetes very often no difference can be found. In cases of a progradient adiposity one finds an abnormally great difference between the sugar curves, the same case showing asthenia under insulin treatment. After a prolonged fast the difference between the capillary and venous blood diminishes.—Josef Charvat.

Paucercatic-ovarian antagonism (*Antagonismo pancreático-ovarico*). Fonseca, F. and C. Trincão, *Compt. rend. Soc. de biol.* 100: 425. 1929.

In man, injections of ovarian extract raise the blood sugar.—J. C. D.

Glycosuria and diabetes. Galambos, A., *Ann. Int. Med.* 2: 1328. 1929.

The author states that not only the inability of the diabetic to oxidize carbohydrate with attendant incomplete oxidation of the fats should be considered but also that the independent metabolic disturbance of protein metabolism should be considered. In severe diabetes mellitus as well as after experimental

removal of the pancreas in dogs, hyperamino-suria is present. The author also believes that in phloridzin diabetes the animal loses the ability to burn dextrose because the R. Q. is low.—E. L.

**Cholesterol in blood of diabetics treated at the New England Deaconess' Hospital.** Hunt, Hazel M., *New England J. Med.* 201: 659. 1929.

The report is based on cholesterol values in 270 diabetic patients and 40 normals. The data are tabulated, analyzed, and summarized. Insulin treatment maintains the cholesterol value within normal limits. These values are lower than in pre-insulin days. Cholesterol values seem a safer guide to the patient's condition than blood-sugar readings.—J. C. D.

**Diabetes mellitus: A further study of the etiology of the disease.** Krantz, J. C., *Ann. Int. Med.* 2: 1209. 1929.

Several other investigators have reported that the blood of a diabetic contains a virus which will produce hyperglycemia and glycosuria. Rabbits were injected intravenously and also subcutaneously with diabetic urine. Though this urine was toxic there was no hyperglycemia or glycosuria. When serum broth which was inoculated with diabetic urine was injected subcutaneously no hyperglycemia or glycosuria was produced. Using the toxicity of urine inoculated broth on the seedlings of *Lupinus Albus* according to the method of Macht, it was shown that the diabetic urine was no more toxic than normal urine.—E. L.

**Studies in crystalline insulin. VIII. The isolation of crystalline insulin from fish islets (cod and pollock) and from the pig's pancreas. The activity of crystalline insulin and further remarks on its preparation.** Jensen, H., O. Wintersteiner, E. M. K. Geiling, *J. Pharmacol. & Exper. Therap.* 36: 115. 1929.

A comparative study of insulin from different sources was made. Methods of preparation are described in detail. Analyses showed close agreement in chemical constitution with beef insulin. Crystals were of the same shape but smaller. Physiological activity was found to be 25 international units per mgm. as compared to 15 units per mgm. in a standard preparation supplied by the Insulin Committee. Preparation of crystalline insulin from pig pancreas was found to be much more difficult than from fish pancreas. The crystals were less uniform, the sulfur content was less, and the yield was smaller. Physiological activity was 20 units per mgm.—C. I. R.

**Insulin and carbohydrate tolerance.** Joslin, E. P., *Ann. Int. Med.* 2: 1001. 1929.

Joslin criticizes the conclusions of Brace, who stated that his five patients lost tolerance under insulin treatment. All of Brace's patients received caloric intake above the need of a healthy adult, which is contrary to the fundamental laws of diabetic dietetics. Joslin has the impression that a diabetic following reasonable rules increases his or her tolerance for carbohydrate. The diabetic of long duration is more apt to die of complications than of coma. In children the diabetic mortality is very low and in patients under 40 years of age it is decreasing.—E. L.

**Eosinophilia in insulin therapy.** Lawrence, R. D. and O. B. Buckley, *Brit. M. J.* 1: 597. 1929.

One of the authors had in 1927 observed a high degree of eosinophilia in a diabetic patient treated with insulin. Twenty insulin treated diabetics were investigated with the result that ten showed an eosinophilia varying between four and twenty per cent. Blood counts on twelve diabetics being treated without insulin as a control revealed no abnormal eosinophilia. They were unable to offer any definite explanation of the finding but suggested three possible ways in which insulin may be responsible: (1) by virtue of its physiological action; (2) as an allergic phenomenon resulting from the protein nature of insulin or from protein impurities in the solution; (3) by reason of the irritative effect on the skin and subcutaneous tissues resulting from the acidity of insulin.—H. C. Shepardson.

Persistent hypoglycemia following diabetes mellitus treated with insulin. Leyton, O., *Proc. Roy. Soc. Med. Clin. Sec.* 22: 71. 1929.

The case described occurred in a male child of 5½ years with a family history of diabetes mellitus on the paternal side. Diabetes was discovered in the child and he was placed upon the proper diet with insulin. The dose of the latter had to be increased to 18 units twice daily. Following the development of a cold, hypoglycemia developed. Thereupon the dose of insulin was decreased slowly until 8 units twice daily were given. At this time severe hypoglycemia developed, which for several weeks threatened the patient's life. Insulin was stopped and in the course of time the symptoms of hypoglycemia subsided. It was observed that during the evidences of hypoglycemia glycosuria occurred nevertheless.—I. B.

Adenoma of the Islands of Langerhaus with associated hypoglycemia. McClenahan, W. U. and G. W. Norris, *Am. J. M. Sc.* 177: 93. 1929.

This is a single case report with four figures. Antemortem studies on the blood sugar showed values varying from 38-42 mgm. At autopsy a nodule 15x7x16 mm. was found on the pancreas. This nodule (adenoma) was found to be composed of island cells. The islands in the remainder of the pancreas were markedly hypertrophied. The authors conclude that there is a definite relationship between such tumors and the observed hypoglycemia.—E. L.

The dietetic treatment of diabetes mellitus. Newburgh, L. H., *Ann. Int. Med.* 2: 645. 1929.

When Allen introduced his diet of high protein, high fat and low carbohydrate, it had a glucose value of 150 grams. Now both Allen and Joslin have modified this diet so that it contains only 80 grams of glucose. Marsh and Newburgh advocated a diet of sufficient caloric value using fat as the chief source of energy and restricting both protein and carbohydrate. The protein must be sufficient to maintain nitrogen balance and the carbohydrate must be ample to insure complete combustion of fat. A typical discharge diet after desugarizing the patient was protein 50, fat 220 and carbohydrate 35. This diet has a glucose value of 86 grams and yields 2300 calories. If this diet is prescribed, about four-fifths of the adult patients will not need insulin. The author does not believe there is any evidence proving or disproving the relationship of diet to arteriosclerosis. This vascular disease is not caused by metabolic products of fat.—E. L.

Regulation of carbohydrate metabolism. Excretion of insulin through the kidneys, and its conditioning (*Regulation des Kohlehydratstoffwechsels. Ausscheidung des Insulins durch die Nieren und ihre Bedingungen*). Partos, A., *Arch. f. d. ges. Physiol.* 221: 562. 1929.

Insulin is a normal constituent of human and rabbit urine. It is not detectable in the urine of fasting rabbits; this explains the production of a higher hyperglucemia of longer duration when fasting animals are fed glucose. During hyperglucemia urine contains no insulin; as soon as the blood-sugar commences to fall insulin is found present. Absorption of carbohydrate is the adequate stimulus for insulin production. After a rich carbohydrate meal the amount of glycogen formed in the liver depends on the amount of insulin previously present. In diabetes mellitus and in experimental diabetes (pancreas extirpation) no insulin is present in the urine. In Sandmeyer-diabetes it is possible to stimulate the islets to insulin production by a rich carbohydrate meal.—A. T. C.

A case of diabetes mellitus showing a glycemia without symptoms. Peters, C. A. and I. M. Rabinowitch, *Am. J. M. Sc.* 178: 29. 1929.

This single case report concerns a diabetic whose blood-sugar at one time was 26 mgm. without any clinical symptoms of hypoglycemia. Consequently, 10 units insulin were injected and no food given. The blood-sugar was determined before and after fermentation. For six hours there was no glucose whatever in the blood, according to the authors. The investigators state that though hypoglycemia is an important factor in the symptoms produced by insulin overdosage, it is not the only factor involved.—E. L.

Action of insulin on the motility of the gastro-intestinal tract. I. Action on the stomach of normal fasting man. Quigley, J. P., V. Johnson and E. I. Solomon, *Am. J. Physiol.* 90: 89. 1929.

Subcutaneous injection of insulin in amounts of 12 to 20 units usually produces in normal human subjects fasting 11 to 44 hours an increase in gastric motility as recorded by the triple balloon method. The essential features of this response are: (a) an increase in gastric tone; (b) type A contractions; (c) a very prolonged hunger period. The gastric hypermotility induced by insulin is not inhibited by smoking, mild nausea, unpleasant emotions, body discomfort, sight or thought of food, extraneous disturbances, swallowing or the presence of indifferent substances or food in the mouth or in the stomach. The gastric motility is inhibited by introduction of dextrose or cane sugar into the duodenum, and also by the subcutaneous injection of atropine or epinephrine. "Insulin sensations," especially hunger, parallel rather closely the degree of gastric activity. Under the experimental conditions described antiperistaltic movements in the stomach were not associated with sensations of nausea.—Authors' Summary.

Fat metabolism in peripheral tissue (*Zur Frage des Fettsstoffwechsels in den peripheren Geweben*). Raab, W., *Wien. Arch. f. Inn. Med.* 17: 439. 1929. *Abst., J. A. M. A.* 93: 1184.

Using Bang's method, Raab determined in man the total purified petroleum benzene fraction, the neutral fat and the free cholesterol in blood from the capillaries and from the veins. He found that in normal persons (in the morning with the stomach empty) the differences between the blood from the capillaries and the blood from the veins are inconstant. The eating of sugar antagonizes the retention of fat in the tissues, causing a mobilization of fat from the tissues to the blood. Insulin inhibits the mobilization of fat. Pituitary extract produces a constant decrease in the neutral fat content of the blood. In the patients with diabetes mellitus in whom lipemia is absent, the differences between blood from the capillaries and blood from the veins are just as little characteristic as in normal persons; in patients with marked lipemia, on the contrary, the venous blood usually contains a great excess of neutral fat. In cerebral and hypophyseal adiposity the fat content is unchanged. In the hyperlipemia that occurs in diabetes mellitus the free cholesterol is only slightly increased; the hyperlipemia consists chiefly in an increase in the neutral fat.

A case of extensive atrophy of the subcutaneous fat following injections of insulin. Rabinowitch, I. M., *Canad. M. A. J.* 21: 67. 1929.

An illustrated case-report showing an extremely marked effect.—A. T. C.

High carbohydrate diets in diabetes mellitus. Richardson, R., *Am. J. M. Sc.* 177: 426. 1929.

Due to inability of patients to absorb completely the fat in high fat diets, the author suggests a diet higher in carbohydrate than that proposed by Newburg and Marsh. The carbohydrate was usually doubled with no increase in insulin. The patients felt better and there were no cases which showed an increased blood-sugar.—E. L.

Insulin resistance and bronze diabetes. Root, H. F., *New England J. Med.* 201: 201. 1929.

No cases of true diabetes have been reported in which insulin failed to reduce the sugar. A relative resistance to insulin may arise as the result of destructive processes in the pancreas, complicating disease of the other endocrine glands, disturbance to the function of the liver, and abnormal processes in the skin and muscles. An extensive bibliography is included.—J. C. D.

Can one differentiate certain glycosurias from the true diabetic glycosurias? (*Besteht gegenwärtig die Möglichkeit, gewisse Glykosurieformen mit Sicherheit von der echt diabetischen zu trennen?*) Salen, E. B. and T. Nyren, *Acta med. Scand.* 70: 330. 1929.

The authors come to the conclusion from their studies that there is but one definite way of differentiating the non-diabetic from the diabetic glyco-

surias, namely, by the means of a glucose tolerance test in which they lay stress on the length of time of the hyperglycemia and pay little or no attention to the height of the curve. Attempts to differentiate between these two glycosurias by means of insulin, they consider as disproven. The renal glycosuria the authors define as follows: "Normal fasting blood-sugar, normal length of postprandial rise after glucose and a lowered threshold."—H. J. J.

Effects of insulin on the endocrine system (*L'influence de l'insuline sur le système endocrine [note préliminaire]*). Schereschewsky and Moguilnitzky, *Rev. franç. d'endocrinol.* 6: 456. 1928.

Post mortem examination of six guinea pigs killed by excessive doses of insulin injected subcutaneously showed an increased size of the suprarenals. Hyperemia was present in the respiratory organs and thyroid, ecchymoses in the kidney, hyperemia and ecchymoses in the stomach and intestinal walls, congestion around the islands of Langerhans. The most characteristic changes were in the adrenals where hyperemia and oedema occurred in the medullary and cortical zones. Both zones showed cellular degeneration. The authors conclude that insulin is not a specific excitant of the vagus, and that its antagonism to adrenalin is of a toxic nature.—B. C.

Isolation of tail of pancreas in a diabetic child. de Takats, G. and R. M. Wilder, *J. A. M. A.* 93: 606. 1929.

An operation was designed to promote hypertrophy of the islet tissue of the pancreas and thereby increase the insulin output from the gland. This operation was performed on a child with severe diabetes with encouraging results.—Authors' Summary.

The effect of parathyroid hormone and increased calcium metabolism on the growth of tumor tissue. Goerner, A. and B. G. P. Shafiroff, *J. Cancer Research*, 12: 294. 1928.

The effect of parathyroid extract on calcium metabolism of normal and tumor-bearing rats was studied. The calcium content of Flexner rat sarcoma was increased but no inhibitory effect due to calcium was obtained. The calcium content of carcinoma number 10 was not increased, there being no difference in growth from the controls.—M. B. G.

Parathyroid tumors and osteitis fibrosa cystica (*Über die Bedeutung der Epithelkörper-vergrössung bei der Ostitis fibrosa generalisata Recklinghausen*). Gold, E., *Mitt a. d. Grenzgeb. d. Med. u. Chir.* 41: 63. 1928.

A case of osteitis fibrosa cystica is described in a female aged 54. A tumor of the right superior parathyroid was removed by operation. Six months later the previously bed-ridden patient was able to walk, showed marked general improvement and a gain in weight of 11 kgm. No change was noted in the bones by Roentgenologic examination. The tumor presented the microscopic appearance of a benign adenomatous hyperplasia of a parathyroid gland. After its extirpation the blood calcium which had previously been elevated as high as 13.1 mgm. per 100 cc. fell to the normal level of 10 mgm. and likewise the urinary calcium which had been twice as great as normal was reduced to a third the normal amount (from 412 to 24 mgm. in 24 hours). The author inclines to the view, previously expressed by Schlangenhauer, Maresch, Gunther and Mandl, that the hyperplasia of the parathyroid is responsible for skeletal disease and is not a secondary compensatory phenomenon as suggested by Erdheim. In support of this interpretation he advances the improvement in his patient and Mandl's following the extirpation of parathyroid tumors. Other significant data are cited. Seventeen cases of parathyroid tumor were observed at autopsy in a period of 7 years. Thirteen of these were associated with abnormality of the skeleton. In 4 no skeletal disturbance was demonstrated. With a single exception only one parathyroid gland was enlarged. In 6 of the 13 cases the anatomical diagnosis was osteomalacia, in 5 generalized osteitis fibrosa cystica, in 1 osteoporosis, in 1 "osteitis deformans, Paget." The diagnosis in the last case was doubtful. On the other hand, in 40 other cases of Paget's disease examined by Maresch there was no single instance of enlargement of parathyroids.—Russell M. Wilder.



The effects of insulin on parathyroidectomized dogs. Reed, C. I., *Am. J. Physiol.* **89**: 239. 1929.

Insulin administration to normal and parathyroidectomized dogs not in tetany will increase calcemia and decrease phosphemia. When in tetany, insulin will relieve symptoms, usually completely, and will produce hypophosphemia. Calcemia responds much less regularly than in normal animals, any increase being followed by a decrease. Tetany alters the effect of insulin on calcemia and to a less extent on phosphemia, but does not affect the post-insulin hypoglycemia curve.—Author's Summary.

Idiopathic or hypoparathyroid tetany in children with special reference to certain psychic manifestations. Shannon, W. R., *Arch. Pediat.* **46**: 346. 1929.

Of the eight cases reported, six responded to parathyroid administration by an amelioration of symptoms and a variable increase in blood calcium. In the remaining two, one of them in a new-born infant, parathyroid extract was not given and calcium determinations were not made. The psychic disturbances noted in this series were present following the convulsions and consisted of mental depression, irrationalism, acute maniac excitation such as screaming, tearing of clothes, fighting with other children and later nightmares and terrors.—M. B. G.

Influence of splenectomy on the testis (Effet de la splénectomie sur la glande génitale male). Kostitch, A. and A. Telebarkovitch, *Compt. rend. Soc. de biol.* **100**: 54. 1929.

In white mice splenectomy, either before or after puberty, does not cause regressive changes in the testis.—J. C. D.

Splenectomy and ovarian function (Effet de la splénectomie sur la fonction ovarienne [cycle oestrien]). Radossavlyévitch, A. and A. Kostitch, *Compt. rend. Soc. de biol.* **100**: 56. 1929.

Splenectomy in white mice at the age of 25-35 days, i.e., puberty, usually produces a precocious appearance of the oestrous cycle as judged by vaginal smears.—J. C. D.

Presentation and action of an active thymus gland extract (Darstellung und Wirkung eines aktiven Thymusdrusenextraktes). Nitschke, A., *Monatschr. f. Kinderh.* **41**: 128. 1928.

Repeated injections of thymus extract produced typical clinical pictures of tetany in 24 to 48 hours in rabbits. The blood calcium showed low values, 5 to 9 mgm. per 100 cc. with an average of 7 mgm. per 100 cc. The author was able to show the tetany productive action of thymus extract on 30 animals, the majority culminating in death. No such manifestations were obtained in the control animals. Thymus extract also has an influence on the metabolism of inorganic phosphorus, as low inorganic P. values in the serum of his experimental animals were obtained. According to the author, thymus extract contains two secretions, one capable of lowering the calcium content and the other the inorganic phosphorus content of serum.—M. B. G.

The treatment of exudative diathesis by means of thymus radiation (Die Behandlung der exudativen Diathese Mittels Thymus Röntgenbestrahlung). Vas, E., *Jahrb. f. Kinderh.* **121**: 293. 1928.

The author found in the majority of children under his observation with exudative diathesis an increase in the thymic shadow as against normal controls. In 38 children with eczema, prurigo or urticaria pigmentosa, he inaugurated thymic radiation. He reports good results especially in children where diatetic and other measures were of no avail. In some of the cases, two or even three treatments by irradiation were necessary.—M. B. G.

Studies on the circulation in Basedow's disease and in cardiac neuroses (Kreislaufstudien beim Basedow und bei der Herzneurose). Bansi, H. W., *Ztschr. f. klin. Med.* **110**: 633. 1929.

This article contains an extensive review of the literature and records, observations on the velocity of the blood stream in Basedow's disease and con-

ditions simulating it. In Basedow's disease and likewise in pre-Basedow's disease the circulation as a whole is arranged uneconomically due to a quicker passage of the blood through the capillaries and an increased venous return to the heart. There is a poor utilization of the oxygen of the blood caused by the uneconomical working of the circulation. The oxygen tension in the venous capillaries was abnormally high in Basedow and pre-Basedow patients, and some of these patients differed from normal individuals by an alteration in the curve of oxygen dissociation, i.e., by having a higher partial pressure of oxygen. The hemoglobin binds the oxygen less closely and as a result gives it up quicker and more easily. The tissues are bathed in fluid with an abnormally high partial pressure of oxygen. The pre-Basedow patients, according to Bansi's observations, are no longer normal in respect to their work ability. In them the quickening of the pulse was associated with an acceleration of the circulation; on the other hand, the blood chemistry, basal metabolism, and usually the work metabolism were normal. This group of individuals, who formerly were grouped with cardiac neurotics, and whom Bergmann classified with those showing stigmata from the vegetative nerves, differ from the psychogenic or neurogenic cardiac neurotics in the fact, that in pre-Basedow's disease demonstrable disturbances of the circulation are found. The cardiac neurosis in general does not have a change in the speed of the circulation, so that the work of the heart is not increased.—W. D. Reid.

**Hyperparathyroidism.** Barr, D. P., H. A. Bulger and H. H. Dixon, J. A. M. A. 92: 951. 1929. Abst., A. M. A.

In the literature on osteomalacia, on multiple cystic tumors of bone and on parathyroid tumors, there is a clinical picture, found occasionally under all of these titles, which seems to deserve description as a separate clinical entity. A survey of the literature revealed some remarkable and little emphasized associations: (1) Few cases of proved multiple giant cell tumors of bone have been reported in the literature. (2) It has been found by many observers that osteomalacia is associated with a negative calcium balance and increased excretion of calcium in the urine. (3) The occurrence of calcium stones and distressing urinary symptoms has been frequently reported in cases of osteomalacia. (4) There have been cases of osteomalacia and other bone diseases in which parathyroid tumors or parathyroid hyperplasia was noted at the time of autopsy. (5) A few cases of osteomalacia have been associated with muscular hypotonia and a complete inability to walk. (6) A high calcium content has been found occasionally in cases which were called osteomalacia and which were associated with multiple cystic tumors of bone. (7) Recent work on parathyroid extract has demonstrated the physiologic changes that occur when there is an excess of the parathyroid secretion. These include (a) hypercalcemia; (b) increased urinary output of calcium and negative calcium balance; (c) depletion of calcium in bone, and (d) hypotonicity of muscle. With the assembling of all the evidence, it seems justifiable to introduce the name of hyperparathyroidism and to consider under this heading the various cases as constituting a clinical entity as definite and distinct as parathyroid tetany or exophthalmic goiter. The clinical features probably are: (1) Rarefaction of bone. (2) The occurrence of multiple cystic bone tumors, several of which on pathologic examination have been found to be giant cell sarcomas. (3) Muscular weakness and hypotonia. (4) Abnormal excretion of calcium in the urine and the formation of calcium stones. (5) Abnormally high serum calcium. All of these changes are secondary to, or associated with, a parathyroid hyperplasia or parathyroid tumor.

**The blood lactic acid range in exophthalmic goiter at rest and after exercise** (Der Blutmilchsäurespiegel beim Morbus Basedow in der Ruhe und Während der Arbeit). Bier, A., Klin. Wchnschr. 8: 1306. 1929.

The blood lactic acid at rest was studied in 12 cases of Basedow's disease, and after exercise in 2 normal individuals, 2 cases of exophthalmic goiter and one case of myxoedema after operation for hyperthyroidism. Determinations were made according to the Mendel-Goldscheider method which gives the upper limit of normal as 15 mgms. of lactic acid per 100 cc. At rest the acid level in exophthalmic goiter was found to be near or above the upper limit of normal (14 to 22.5 mgms. per 100 cc.). After exercise (stair climbing) the blood lactic acid in the normal cases rose slowly and fell to the normal resting level

within 6 minutes. In the two hyperthyroid cases the rise was much steeper, reached a higher level (37.5 and 40.5 mgms.) and returned to the resting level after a longer interval. In myocardial insufficiency Eppinger has reported high and prolonged lactic acid curves after exercise. Bier points out that the lactic acid rises more slowly in cases with cardiac disease than in cases with hyperthyroidism. After thyroidectomy the lactic acid curve was similar to the curves in the two normal cases. Oxygen consumption was found to be increased in proportion to the increase in blood lactic acid in hyperthyroidism.

—D. P. Foster.

**Unusual forms of hypothyroidism:** (1) mild myxedema in two sisters; (2) severe menorrhagia due to hypothyroidism; (3) severe metrorrhagia due to hypothyroidism; (4) mild myxedema in a patient with constitutional autonomic dysfunction; (5) end result of cretinism after 16 years of continued thyroid treatment. Blumgarten, A. S., *M. Clin. N. Amer.* 12: 593. 1928.

Typical hypothyroidism occurs in two forms; adult hypothyroidism or myxedema and infantile myxedema or cretinism. The symptomatology is the same in both, with the exception that disturbances in growth and mental development occur in the infantile form in addition to the cardinal symptoms of the adult form. Although a careful examination of the myxedematous patient will reveal changes in the various systems of the body, the outstanding symptoms are the skin changes, the circulatory symptoms, and the typical mental sluggishness. When, however, the disturbances in other systems dominate the clinical picture, the hypothyroid etiology becomes obscure. The most common chief complaints in most of the atypical forms of myxedema are the following: rheumatoid pains; severe menorrhagia or metrorrhagia; anemia; obesity; a sensation of pressure on top of the head and severe atonic constipation.—I. B.

**Treatment of Basedow's disease (Zur therapie des Morbus Basedow).** Bonem, P., *Schweiz. Med. Wchnschr.* 30: 764. 1929.

Despite the value of thyroidectomy in Basedow's disease, the risks entailed should not be overlooked. Medical measures to control symptomatology include bromides, possibly with valerian and quinine hydrobrom. Arsenic and gnygergen are also useful. Digitalis is useless, but strophanthus or convallaria may be employed if such a drug appears indicated. Iodine therapy is a debatable question and generally does more harm than good. These patients do well at an elevated location of about 3000 feet, where the air is cool and rare. The use of insulin to improve carbohydrate tolerance and increase food intake is still a matter of question. The x-ray experiences of the author are favorable.

—I. B.

**Reactive hyperthyroidism in calculous pyelitis (Hyperthyroidisme reactionnel par pyélite lithiasique).** Bonilla, E. and S. Ferrero Velasco, *Rev. franç. d'endocrinol.* 6: 370. 1928.

The authors emphasize the importance of focal infections in cases of hyperthyroidism characterized by continuous low grade hyperthermia. They describe a case absolutely intractable to classic methods of treatment. The persistence of slight fever led to a search for focal infection and the finding of a small renal calculous, with pyelitis. After elimination of this focal infection the hyperthyroidism disappeared. The authors maintain that hyperthermia of the type discussed is a contraindication to surgical treatment for the hyperthyroidism until the focal infection is cleared up.—E. B.

**Tuberculosis of the thyroid gland.** Budd, S. W. and C. Williams, *J. A. M. A.* 92: 1741. 1929. *Abst., A. M. A.*

The three cases of tuberculosis of the thyroid reported on by the authors had much in common from both the clinical and the pathologic points of view. The patients were all women of approximately the same age (average, 41 years); all complained of soreness and tenderness in the region of the thyroid of a few months' duration; all three had slightly elevated temperatures and accelerated pulse rates; two had lost weight (average 20 pounds); all were nervous, and two had increased basal metabolic rates. No positive signs of other tuberculosis were found in any of them, but one had had bronchitis for several years, and another had the scar of a cervical abscess and a chronic anal

fistula. Pathologically all had the fibrous type of tuberculosis, which is the most unusual manifestation of the disease. The wounds healed in from two to four weeks; all gained weight (average, 10 pounds), and the general symptoms were largely relieved. Their first patient was suspected of having malignant condition until a frozen section clarified the diagnosis. The second patient seemed to have an acute pyogenic infection and operation was delayed. The third case was diagnosed properly prior to operation.

**Thyroid and cerebral activity** (*Thyroïde et activité cérébrale*). Cardot, H., J. Regnier, D. Santenaise and P. Vare, *Rev. franç. d'endocrinol.* 7: 89. 1929.

Researches and clinical experience seem to indicate that some sort of a relationship exists between the activity of the pneumogastric and certain endocrine glands, and the regulation of cerebral activity. In order to test this theory the authors attempted to make parallel studies of the excitability of the pneumogastric center and a motor center of the brain. Using among others the oculo-cardiac reflex as an indicator, functional relations between the pneumogastric and the sigmoid gyrus were demonstrated. The study of the thyroid relation is treated in a later paper.—B. C.

**The effects of ingestion of thyroid upon the thymus, testicle and thyroid** (*Action de l'ingestion de corps thyroïdes sur le thymus sur le testicule et sur la thyroïde*). Courrier, R., *Rev. franç. d'endocrinol.* 6: 10. 1928.

The writer shows experimentally that when white rats are fed fresh thyroid tissue, there is a recession of the thymus when insufficient food is present for maintenance of body weight, but that there is no recession if the food supply is adequate. He reaches similar conclusions regarding the testicles. The opposite effects reported by others he attributes to malnutrition. His experiments on the effects on the thyroid gland were carried out on dogs and cats. In these experiments ingestion of thyroid produced involution of the thyroid. There is a discussion of the clinical significance of the experiments.—(Corrected Abst.)—B. C.

**Myxedema** (presumably) confined to the palate and larynx. Dundas-Grant J., *Proc. Roy. Soc. Med. Clin. Sec.* 22: 61. 1929.

A woman aged 20 complained of thickness of the voice, soft stridor on inspiration and occasional dysphagia and general debility. Examination revealed a thickening of the soft palate and uvula, and enormous pale infiltration of the epiglottis almost completely concealing the rest of the larynx. White shiny edema of both ary-epiglottic vaults was present and only an occasional glimpse of the exterior part of the right vocal cord was obtainable. A diagnosis of localized myxedema was made, which was confirmed by very good results obtained from thyroid opotherapy.—I. B.

**Osteoporosis secondary to hyperthyroidism.** Dunlap, H. F. and A. B. Moore, *M. Clin. North America*, 12: 1511. 1929.

Hyperthyroidism due either to exophthalmic goiter or to toxic adenoma and the elevation of the basal metabolic rate by administration of thyroid extract or of thyroxin, are associated with increased calcium excretion, i.e., a greater calcium output than intake, hence a negative calcium balance. A similar phenomenon but to a lesser degree occurs with phosphorus. Osteoporosis occurring in hyperthyroidism was studied with the roentgen rays. The condition affects all the bones but when of moderate or slight degree it is most readily discerned in the spongy bones and those with superficial coverings, such as the skull, ribs, and bones of the extremities. In the long bones it is likely to be most apparent in epiphyses and ends of the diaphyses. The loss of calcium varies in degree from mere increase of translucence, so trivial that it may escape notice, to marked and unquestionable rarefaction. The degree of decalcification appeared to be in direct ratio to the severity and duration of the hyperthyroidism. This is substantiated in the five cases recorded in this paper. In the first case the hyperthyroidism, although severe at the time of admission, had not been prolonged; in the second case, hyperfunction of the thyroid gland had existed only a year. In both cases the osteoporosis was only moderate at most. The last three cases exemplify an intense and enduring

hyperthyroidism with a proportionate absorption of calcium, the latter being so pronounced that the question of metastatic malignancy was raised in two of the three cases.—I. B.

**Basedow's disease accompanied by vitiligo and paroxysmal tachycardia** (*Maladie de Basedow, vitiligo et tachycardie paroxystique en evolution combinee*). Etienne, G. and Bequain, *Rev. franç. d'endocrinol.* 6: 427. 1929.

A case of Basedow's disease is reported in which a symmetrical development of pigment occurred as in Addison's disease. Favorable response to thyroid treatment, with loss of pigment was observed. The author holds that the sympathetic is probably involved either directly or indirectly through the action of the suprarenal or possibly the thyroid hormones.—B. C.

**Influence of internal secretions of vertebrates on invertebrates** (*Zur Frage der Beeinflussung Wirbelloser durch Wirbeltierinkrete*). Fleischmann, W., *Arch. f. d. ges. Physiol.* 221: 591. 1929.

Review of the literature suggests that parenteral introduction of thyroid preparation has no action on the metamorphosis of insects, whence it may be concluded that such action is only to be expected in animals possessing a thyroid, or at least homologous tissue.—A. T. C.

**The use of vitamins A and D and sodium iodide in the pre-operative treatment of Graves' disease.** Fraser, R. H. and A. T. Cameron, *Canad. M. A. J.* 21: 153. 1929.

A combination of vitamins A and D and sodium iodide produces the same beneficial effect as "vitiodum" and as Lugol's solution in the pre-operative treatment of Graves' disease. Further evidence has been obtained that the mixture of the two vitamins (without some form of iodine) is without action. —A. T. C.

**Thermal cures and the thyroid gland** (*Cures thermales et glande thyroïde. Etat actuel de la question Premières recherches personnelles*). Galup, M. J., *Rev. franç. d'endocrinol.* 7: 128. 1929.

Improvement under medication with certain thermal waters of cases evidently due to thyroid difficulty leads the author to believe that the results are due to direct effects upon some of the endocrine organs, possibly the thyroid. He does not believe that the results are due to the radio activity of the water. —B. C.

**Injury resulting from radiation in Basedow's disease.** Goette, K., *Proceedings of the Department of Roentgenology*, 39: Heft 1. 1929. *Abst., Arch. Physiol Therapy*, 10: 137. 1929.

A consideration of the course of two cases of moderately severe Basedow's disease, which after radiation ( $\frac{1}{4}$  Hed., the other twice,  $\frac{1}{10}$  Hed.) became considerably worse and died with the symptoms of hyperthyroidism. The aggravation of symptoms must be attributed to the radiation. Radiation therapy also as surgery in true Basedow's disease, is not without risk.

**Roentgen irradiation in treatment of hyperthyroidism.** Groover, T. A., A. C. Christie, E. A. Merritt, F. O. Coe and E. M. McPeak, *J. A. M. A.* 92: 1730. 1929. *Abst., A. M. A.*

A statistical evaluation of roentgen irradiation in the treatment of hyperthyroidism based on 305 cases is made by the authors. In this series there were 26 cases in which a thyroidectomy had previously been performed, without improvement, with incomplete relief, or with recurrence of toxicity. The results of treatment were: cured of hyperthyroidism, 271, 88.85 per cent; improved, twenty-six, 8.52 per cent; unimproved, eight, 2.63 per cent. One of the most reliable criteria for judging progress in cases of hyperthyroidism is the weight curve. The greatest gain in any single case of their series was 80 pounds (36 Kg.). One of the criticisms that has been made with respect to

the irradiation of hyperthyroidism has been the length of time required to gain improvement or to effect a cure. On an average, 6.6 treatments per patient were administered in this series of cases, and generally 2.7 treatments were given before improvement was first noted. As cases are treated at intervals of three weeks, it is apparent that the average duration of treatment was less than five months and the average lapse of time before improvement began was approximately two months. The authors have not been able to determine from their records the average loss of time from work by the patients of this series, but they have every reason to believe that the economic loss from this source has not been greater than with any other adequate method of treatment, and, on the whole, has probably been less. In this series symptoms of hyperthyroidism on an average antedated the beginning of roentgen treatment more than two years. While the facts and figures given do not justify any final conclusion as to the permanence of cure following roentgen therapy, they at least indicate that results in this regard are quite as satisfactory as with any other method. Among the factors which have contributed to failures to cure hyperthyroidism by radiation therapy, are the following: (1) overwhelming toxicity; (2) serious cardiovascular or other visceral changes, and (3) noncooperation on the part of the patient or the attending physician. As twenty-six patients had had previous thyroidectomies without cure the results of roentgen therapy in this group are slightly more favorable than they are for the entire series, but the difference is not sufficient to be regarded as significant. Five deaths have occurred in the group of 271 cases recorded as cured of hyperthyroidism, as follows: organic heart disease, two; cerebral hemorrhage, one; tuberculous laryngitis, one; unknown, but not due to hyperthyroidism, one. Telangiectasis of the skin is a sequel of roentgen therapy that needs always to be kept in mind. It occurred in six cases, mostly in cases in which there was a departure from the standard technic as to dosage.

Creatinuria as a sequel to fractures of bones and the influence of thyroid feeding upon it and upon the creatinuria of post-encephalitic rigidity. Hirst, Marion and C. G. Imrie, *Quart. J. Med.* 22: 153. 1928.

The authors summarize from their study of four patients with fractures, that creatinuria occurred after fractures of bones. The administration of thyroid extract increased the output three fold in a case of fracture of the femur. The excretion was most marked at night. The increase in the output of creatinin preceded any change in basal metabolism or any other nitrogenous constituent of the urine. Blood creatinin was not increased and the uric acid showed only a slight rise. The creatinuria of the Parkinsonian rigidity was practically uninfluenced by administration of thyroid extract in amounts which caused a similar increase in total nitrogenous excretion and basal metabolism to that brought about in the case of fracture of the femur. A diuresis was observed in each case as a result of taking thyroid.—R. C. Moehlig.

The question of iodine in the investigation of goiter (*Die Jodfrage beim Kropfproblem*). Jansen, W. H. and F. Robert, *Deutsches Arch. f. klin. Med.* 157: 224. 1927.

This paper discusses the iodine content of the goitrous thyroid and of the blood in goiter patients and their relation to thyroid function and toxicity. The total iodine content is greater in the goitrous thyroid than in the normal thyroid but the relative iodine content is less. Deficiency of iodine containing foods leads to deficiency of blood-iodine and of iodine concentration in the thyroid; this serves as a stimulus to goiter formation. The toxic thyroid usually shows a relatively low iodine concentration, and the Basedowian goiter particularly has a smaller absolute iodine content despite the common presence of an increased blood iodine. The Basedowian goiter may impoverish itself of its hormone by pouring it out in excess into the blood. The iodine concentration of thyroid tissue and the blood iodine content cannot, however, be taken as an index of the degree of thyroid dysfunction, since in many cases of Basedow's disease not only a lower iodine content in the goiter but a normal blood iodine content is found. The quantitative iodine aspect alone, whether in thyroid or blood, is not a reliable indication of the degree of thyroid activity. Apparently favorable alteration of the iodine content of thyroid tissue and of the blood by the administration of iodine by no means yields uniform results. While in some instances improvement is noted, in others no effects are ob-

served and in still other instances iodine-Basedow symptoms are produced. It therefore appears that iodine chemistry governs the study of thyroid physiology more from a qualitative than a quantitative aspect.—I. B.

**Familial occurrence of congenital myxedema (Familiäres Auftreten von Kongenitalem Myxodem).** Johannsen, N., *Acta paediat.* 7: 179. 1928-29.

Of 5 sisters, 3 showed symptoms of internal secretory disturbances which could be attributed to a hypothyroidism. One came under observation at one year of age but in spite of many years of treatment became idiotic. The second was seen a few months after the appearance of initial symptoms, and placed under treatment with thyroid extract with beneficial results. The third sister died at the age of one year from what was evidently a myxedematous condition. The early symptoms of congenital myxedema are constipation, persistence of a low body temperature and hypertrophy of the tongue.—M. B. G.

**Seasonal and geographical variations in the iodine and thyroxine content of the thyroid gland.** Kendall, E. C., *Tr. A. Am. Physicians*, 43: 143. 1929.

Kendall's results confirm the views of Seidell and Fenger that there is a marked seasonal variation in the iodine content of thyroid glands of beef, sheep and swine. Indeed, there is almost 300% variation in the total iodine content in 100 pounds of hog thyroid. The amount in January and February may approach 14 gm. in each 100 pounds, and the amount in August and September may be as high as 38 gm. The percentage distribution of the iodine containing compounds in the thyroid is affected by geographical distribution and it has been shown by Martin that the iodine content of the thyroid glands of sheep grown in England does not vary with the season. The most important factors are probably the diet, the amount of sunshine, the temperature and the iodine available in food. Also the percentage of total iodine in the form of thyroxine may be greatly influenced by changes which occur after the gland has been removed from the animal. Thyroxine possesses qualitatively all of the activity of the gland. The maximal percentage of the total iodine which can be separated as crystalline thyroxine is not more than 15%. Thyroxine appears to represent an intermediate form of the active constituent. The physiological activity of the thyroid gland appears to be due to active thyroxine.—I. B.

**The enlarged thyroid in school children (Zur Frage der grossen Schilddrüse bei Schulkindern).** Kirsch, O., *Klin. Wchnschr.* 7: 2157. 1928.

Based upon a study in Wien, Kirsch agrees with the conclusions reached by Samuelson that the diminution in size of the enlarged thyroid is not dependent on iodine administration but on the improvement in general living conditions, especially in the diet. The best prophylactic agent against goiter is a diet rich in animal protein.—M. B. G.

**Studies on thyroxin (Thyroxinstudien).** Kornfield, W. and E. Noble, *Klin. Wchnschr.* 1: 2377. 1928.

Guinea pig experiments showed that thyroxin is from 100 to 200 times as effectual as dry thyroid extract. The therapeutic dose for a child, 50 cm, sitting height is  $\frac{1}{4}$  mgm. daily and for one 70 cm. S. H. is  $\frac{1}{2}$  mgm. The effect of thyroxin as well as that of dry thyroid extract is dependent to a great extent on the diet and general nutritional state of the patient.—M. B. G.

**The effect of thyroid on the growing organism (Die Wirkung der Schilddrüse auf den Wachsenden Organismus).** Lukacs, J., *Jahrb. f. Kinderh.* 121: 289. 1928.

Thyroid gland was fed to white rats producing an experimental thyrotoxicosis. It was found that the thyroid feeding did not increase the growth under the optimal growth conditions of the animal but when an individual dose was exceeded, an exacerbation in growth occurred. The bones of such thyrotoxic animals showed an osteoporosis. The relative tolerance to thyroid of young animals could be determined but the tolerance was in no way related to the intensity of the bone changes. The thyrotoxic symptoms were also noted in nursing animals, the thyrotoxicosis being transmitted through the milk of the mothers.—M. B. G.

The influence of the thyroid gland on the action of morphine. Lund, C. C. and E. B. Benedict, *New England J. Med.* 201: 345. 1929.

Data on the effect of morphine on the metabolism of four rabbits are presented. Each rabbit was observed in the normal, hyperthyroid, and hypothyroid states. A large dose of morphine caused a drop of about 10% in the metabolism of the normal rabbit. The same dose of morphine caused a drop of 20% in the metabolism of a hypothyroid rabbit. No change was produced by the same dose of morphine on the metabolism of the hyperthyroid rabbit. The rate of metabolism of hypothyroid rabbits after a dose of morphine was extraordinarily constant.—J. C. D.

The body temperature in hyperthyroidism (Contribucion al estudio del comportamiento de la temperatura en el hipertiroidismo). Maraño, G. and E. Bonilla, *Med. ibera* (No. 534), 113. 1928.

In the various types of hyperthyroidism prolonged low-grade fever is very frequently seen. In a large proportion of cases it is possible to demonstrate the existence of a latent focal infection. In all such cases such foci should be sought for. Lucatello has made the observation that in the hyperthermia of hyperthyroidism the axillary temperature is higher than the rectal. In 17 cases of hyperthyroidism the authors have made comparative studies of axillary and rectal temperatures after a half hour of repose and after 1500 meters of moderate walking. In a considerable number of these cases they also determined the basal metabolism in repose and after exercise. In every case of hyperthermia in repose they have found a focus of latent infection. In two only was the sign of Lucatello confirmed and in those two cases the increase of the axillary temperature was slight. There was no relationship between the temperature in repose and the intensity of the hyperthyroidism as judged by clinical symptoms or basal metabolism. After exercise the temperature of the hyperthyroid subjects increased about as in normal individuals. The temperature curves after exercise in three cases studied did not differ significantly from the normal. The basal metabolism increased always after exercise in varying degrees.—E. B.

Influence of thyroidectomy in the parents on the weight of the thyroid in their offspring (Influence de la thyroïdectomie des parents sur le poids de la thyroïde des descendants).

Histological changes in the glands of animals descended from thyroidectomized parents (Modifications histologiques de la glande thyroïde des animaux nés de parents éthyroïdés). Marza, E. and V. Marza, *Compt. rend. Soc. de biol.* 101: 234, 236. 1929.

There is a slight reduction in size and weight of the thyroid glands of new born guinea pigs from thyroidectomized parents. Histologically, the differentiation of the glands is retarded.—J. C. D.

Noto on the experimental production of lymphadenoid goiter in rats. McCarrison, R., *Brit. M. J.* 1: 5. 1929.

On a diet of American white flour 72 to 80 parts, meat residue 5 to 15, olive oil 8, salt mixture (0.45% potassium iodide) 5, distilled water ad lib., 25% of young rats showed goiters in from 75 to 165 days on post-mortem examination. They occurred more frequently in females. The glands were from 2 to 5 times the normal size. The histological features were those of lymphadenoid goitre. As an unsuitable diet containing sufficient iodine is causal in rats, a similar etiology is likely in man.—Wm. Susman.

Hypothyroidism without myxoedema; its recognition and treatment. McKean, R. M., *J. Michigan M. Soc.* 28: 128. 1929.

This classification was given to a group of fifty ambulatory patients on the basis of the close approach of many of their symptoms and signs to those in Kocher's original classification of true myxoedema and a like response to thyroid therapy, yet with a complete absence of the non-pitting oedema so characteristic of that affection. With basal metabolic readings lower in many instances than the myxoedema case, with the frequent occurrence (52%) of a



body weight at or below the normal level, and other factors similarly variant, it seemed to the author that we are dealing with a decidedly common clinical entity differing not so much quantitatively as qualitatively, and suggesting that some different process has gone on in the thyroid gland of such patients than in that of the myxoedemic. The nature of this change and its etiology is undetermined, but chronic infections, particularly of the upper respiratory tract, and possibly the routine use of iodized table salt, seem to play a part. The characteristic symptoms and signs of this group are presented and its treatment outlined.—Author's Abst.

**Thyroid deficiency as a cause of poor health.** McLester, J. S., *M. Clin. North America*, 12: 1357. 1929.

The patients in this group presented disabilities which can best be described merely as "poor health"; not the well defined, easily recognized characteristics of thyroid deficiency of high degree. The salient characteristic is lack of endurance, sometimes called chronic nervous exhaustion,—an inability to resist or endure physical or mental strain. However, there is no impairment of the patient's reasoning powers,—he is merely incapable of consistent mental effort and is lacking in initiative. Numbness and vague pains in arms and legs, occasionally chronic joint pains, frequently constipation and vague digestive disturbances, are complained of. Though occasionally there is puffiness about the eyes, the appearance is not that of typical myxedema. Occasionally, not always, there is obesity. Frequently the muscular development is poor, giving the appearance of flabbiness. Some patients are actually underweight,—victims of undernutrition and lowered metabolism. The patient often looks tired but in conversation may brighten up and for a time show normal interest and enthusiasm. Characteristic symptoms of the circulatory apparatus are slow pulse and low blood pressure, and frequently there is a bottle-shaped heart. Low grade secondary anemia is frequently found,—otherwise there is nothing noteworthy about the blood. The urine often contains albumin. Many of these patients are erroneously believed to have nephritis and are treated for this disease. The basal metabolism is always low and furnishes the final criterion by which the patient is judged. All of the patients in this group have had a basal metabolism of 15% or more below the calculated normal. Often it was minus 20 to minus 30%.—I. B.

**On the nature of the iodine reaction in exophthalmic goiter; with particular reference to the effect of iodine late in the course of the disease.** Means, J. H., W. I. Thompson and P. K. Thompson, *Tr. A. Am. Physicians*, 43: 146. 1929.

Iodine response is observed in any stage of exophthalmic goiter, provided the patient is not already receiving iodine. When iodine is continued beyond the 10-day period indicated the metabolism may remain on a level for a time and then may rise slowly. When iodine is omitted it usually rises abruptly. In other words, although iodine in relatively large doses seems to have the power markedly to modify the intensity of thyrotoxicosis in exophthalmic goiter, the authors have no evidence to show that the drug can alter the natural duration of the disease. In chronic or prolonged exophthalmic goiter the response to iodine is especially illuminating. In a number of instances after years of continuous thyrotoxicosis there occurs just as sharp fluctuations in symptoms and metabolism upon the giving or omitting of iodine as those encountered early in the course of the disease.—I. B.

**Congenital syphilis of the thyroid gland.** Menninger, W. C., *Am. J. Syph.* 13: 164. 1929.

Three autopsied cases of congenital syphilis showing lesions in the thyroid gland and one clinical report of hypothyroidism in a congenital syphilitic girl are reported. Both hypothyroidism and hyperthyroidism occur with congenital syphilis and in some cases are unquestionably a part of the syphilitic process. Hypothyroidism is more frequent and probably results in most cases from the effect of an intrauterine toxin becoming manifest at an early age. Hyperthyroidism is more probably the result of the localization of infectious processes in the gland and usually does not become evident before adolescence. Pathologically the thyroid may be normal, larger or smaller in size. Several

cases of gummatous formation have been reported. Spirochetes may or may not be present.—M. B. G.

Tachycardia and hyperthyroidism; report of 3 cases without evident enlargement of the thyroid gland or exophthalmos. Mohler, H. H., M. Clin. North America, 12: 975. 1929.

Three cases are reported in which tachycardia was an outstanding symptom due to a toxic thyroid gland without evident enlargement. In two of the three cases the tachycardia was associated with a damaged heart, but with no other evidence of congestive heart failure.—I. B.

The intracutaneous salt-solution test in thyrotoxicosis. Mora, J. M., Am. J. M. Sc. 177: 219. 1929.

Intracutaneous salt tests (0.2 cc. of 0.85% sodium chloride injected intradermally) were made before and after operation in 42 cases of thyrotoxicosis. The time of disappearance of the wheals varied from 15 to 55 minutes, depending on the degree of thyrotoxicosis. In a normal individual the wheal disappears in 60 minutes or more. After operation the time of disappearance was normal.—E. L.

Standardization of thyroid preparations. Morch, J. R., J. Physiol. 67: 16. 1929.

A review of methods previously employed and description of a new method based on CO<sub>2</sub> production is given. Experimental conditions were standardized. The proposed unit is the amount by weight of thyroid preparation given by mouth to white mice daily for 3 weeks and calculated per 1000 gm. of mouse, that will cause a 15% increase in CO<sub>2</sub> production. Six different preparations of dried thyroid varied from 10 to 100 units per gram by this test, demonstrating the necessity for standardization.—C. I. R.

The Basedowian neurosis and its relation to a special form of neurosis with paroxysmal tremors (*Sobre las neurosis Basedowoides y su relacion con una forma especial de neurosis tremorosa paroxistica*). Novoa Santos, R., *Progresos de la clínica*, 36: 176. 1928.

It is difficult to establish the line of division between typical exophthalmic goitre and those dystonic vegetative disorders designated as Basedowian neuroses. The author has observed five cases of neurosis with paroxysmal trembling which closely resemble an intense febrile chill. All the subjects during intervals between crises showed dystonic symptoms and three showed symptoms of the Basedowian type except exophthalmos. Two of these latter had moderate tumefaction of the thyroid.—E. B.

The function of the thyroid gland containing adenomatous tissue. Plummer, H. S., *Tr. A. Am. Physicians*, 43: 159. 1929.

The conclusions drawn by the author are as follows: (1) diffuse hypertrophy and localized hypertrophy are not, in general, part of the same disease process; (2) exophthalmic goiter and adenomatous goiter with hyperthyroidism are distinct entities; (3) the hyperthyroidism of exophthalmic goiter is caused by hyperfunction of the entire thyroid gland; (4) it is probable that the hyperthyroidism of adenomatous goiter is caused by a localized reaction in the thyroid gland and is only an incident in the course of endemic goiter.  
—I. B.

The effects of iodine treatment, with and without vitamins, on the basal metabolic rate in exophthalmic goiter. Rabinowitch, I. M., *Canad. M. A. J.* 21: 156. 1929.

Thyroids from goitrous patients are not lacking in iodine, and when iodine has been administered large amounts may be found in the thyroid tissue. Lack of iodine would seem to be not the only factor responsible for the clinical signs and symptoms of Graves' disease. Administration of a combination of

vitamins A and D and an iodized fatty acid to 12 patients suffering from Graves' disease produced in each case a marked fall in the basal metabolic rate, the average decrease per day being somewhat greater than that in 12 other patients given Lugol's solution.—A. T. C.

**Cardiovascular disease associated with nontoxic goiter.** Rose, E., *M. Clin. North America*, 12: 1157. 1929.

The incidence of cardiovascular disease is greater in patients with so-called simple or nontoxic enlargement of the thyroid than in the average general population. This applies particularly to the later decades of life in goiter belts. The manner in which such cardiovascular damage may be produced is not known. It would seem possible that goiter not capable of producing the syndrome of hyperthyroidism in the generally accepted sense of the term might nevertheless produce an agent capable of injuring the myocardium and vascular apparatus. A further reason for the energetic treatment of simple goiter is presented and the prophylactic value of surgical removal of thyroid enlargements in adult life is suggested.—I. B.

**On the treatment of exophthalmic goiter with antithyroidin.** Rud, E., *Acta Med. Scandinav.* 72: 274. 1929.

Nine patients with exophthalmic goiter were treated with antithyroidin. With the exception of one case, the treatment lasted 6 to 8 weeks. Five of the patients were treated with antithyroidin-moebius (Merck), 4 with tablettae antithyreoidinini (State Serum Institute, Copenhagen). During the treatment with antithyroidin, or in immediate connection with, there was not observed any improvement of the objective findings (basal metabolism, etc.) apart from what might naturally be due to the general treatment. This applied to antithyreoidin-moebius as well as to tablettae antithyreoidini.

—Author's Summary.

**Cardio-renal syndrome and hypothyroidism.** Sainton, P., E. Doumer and P. Veran, *Ann. de méd.* 24: 513. 1928.

The relief of some cases of edema as a result of the administration of thyroid has led certain authors to consider the origin of dropsical syndromes to be extrarenal and to revise the pathogenesis of edema. The authors of the present article cite recent reports of observers who have removed edema by thyroid extract and found it to return on cessation of the medication. During the edematous stage the tests of renal function were practically normal. Also there was present marked hypercholesterinemia and a hypoproteinemia, inducing a diminution of the osmotic pressure in the interior of the capillaries where the osmotic exchanges occur. The history of a woman aged 45 years is reported in considerable detail. Until the age of 38 years she was subject to various disturbances; sudden swooning, attacks of migraine, urticaria of the type known as "Quinck's edema," spontaneous ecchymoses, intermittent albuminuria, amenorrhea following a pregnancy in the course of which attacks of tetany occurred. At the age of 38 years she presented in the hospital a severe picture of chloride, uremic, and hypertensive nephritis with a dilated and insufficient heart, resisting absolutely the customary treatment and suggesting a grave prognosis of early death. The patient left the hospital unrelieved. She found by herself and by accident that thyroid extract remedied her condition. She took it in large dosage and recovered rapidly. She has remained for the past seven years in a satisfactory state of health, only by the influence of thyroid medication. From the first this patient presented very clear signs of hypothyroidism: intellectual apathy, tendency to somnolence, chilliness, constipation with signs of muco-membranous colitis, disturbance of the libido, and even amenorrhea. The tests for renal function showed renal insufficiency. All of the foregoing and the edema disappeared rapidly subsequent to the taking of thyroid extract. More recently the tests for renal function show very slight abnormal findings though the patient is clinically well and using an adequate amount of the thyroid extract. These observers believe that the kidneys have finally incurred some permanent injury. The patient likewise displayed an extreme sensitiveness of her skin to light and purpura during the periods of hypothyroidism. The authors conclude that certain cardio-renal patients are merely hypothyroid individuals whose hearts, as well as the kid-

neys, can regain their functional integrity when edema disappears under thyroid medication.—W. D. Reid.

Difference in effect of feeding goitrous material and normal thyroid to chickens (*L'hyperstrumisation chez les Gallinacés, son action différente de l'hyperthyroïdisation*). Sainton, P. and H. Simmonet, *Compt. rend, Soc. de biol.* 100: 550. 1929.

Goitrous material from patients showing no hyperthyroid symptoms was dried in the cold. When this was fed to chickens, the usual changes in plumage which follow thyroid feeding failed to develop. Sufficient iodine was added to the material fed to bring its iodine content up to that of normal thyroid without changing the results.—J. C. D.

The enlarged thyroid in school children (*Zur Frage der grossen Schilddrüse bei Schulkindern*). Samuelson, S., *Klin. Wchnschr.* 7: 1567. 1928.

Upon the basis of observations of 109 boys and 201 girls in Breslau the author concludes that the administration of iodine does not influence growth of the thyroid. The improvement in the general well-being which occurred simultaneously with the administration of iodine is due to other conditions, especially that of nutrition.—M. B. G.

Endocrine aspects of scleroderma; report of a case with glandular dysfunction. Seale, E. R., *South. M. J.* 22: 885. 1929.

A report with discussion of the case of a girl of 15, who showed improvement under treatment with thyroid and ovarian extract.—J. C. D.

The thyroid and headache at the menopause. Stevens, N. C., *New England J. Med.* 201: 168. 1929.

The author concludes that there is a definite symptom complex occurring in women between the ages of forty-five and sixty, which is characterized by headache, fatigue, nervousness, subnormal temperature, dry skin, sensitiveness to cold, and a low normal or subnormal basal metabolic rate. Such patients are benefited by the administration of thyroid extract.—J. C. D.

Effects of thyroid preparations upon the spontaneous contractions of the guinea pig uterus (*Einfluss der Schilddrüsenpräparate auf die Spontankontraktion des Meerschweinchen-uterus*). Toth, A., *Endokrinol.* 2: 94. 1928.

Thyroid gland fed over a period of time and in sufficiently large doses increases the spontaneous contractions of the uterus up to as much as 100%, and at the same time changes the type of the curve. Thyroxin injections do not give any such results although definitely increased contractions were observed when the thyroxin was added directly to the Ringer bath. Serum filtrate from injected animals did not give the same curve as that of thyroid fed animals. Attention is called to the similarity of the actions of the ultrafiltrate and hypotonic sodium chloride solution.—B. C.

Hyperthyroidism and castration. Changes in weight of bones and other organs (*Hyperthyroïdisme et castration. Modifications pondérales des os et des différents organes*). Trifon, Nina, *Compt. rend. Soc. de biol.* 101: 615. 1929.

Body weight and weight of bones increased most rapidly in hyperthyroid animals, then in order in spayed animals receiving thyroid feedings, in controls, and in spayed animals. The thyroid gland grew most rapidly in spayed and least rapidly in hyperthyroid animals. The adrenals grew largest in controls, next in spayed, next in hyperthyroid animals, and were smallest in spayed hyperthyroid animals.—J. C. D.

Changes in sedimentation speed of erythrocytes in thyroid diseases (*Veränderung der Senkungsgeschwindigkeit roter Blutkörperchen bei Schilddrüsenerkrankungen; vorläufige Mitteilung*). Tschernosatonkaya, E. P., *Klin. Wchnschr.* 8: 791. 1929. Abst., *J. A. M. A.* 93: 246.

Experiments were made on thyroidectomized sheep and rabbits and also on sheep which had received thyroid preparations. The sedimentation speeds

in fifty patients with thyroid disturbances were also determined. All patients with hyperthyroidism showed a considerable increase in the sedimentation speed, while in patients with hypofunction of the thyroid this was decreased. The changes in the sedimentation speed were in direct proportion to the severity of the disease. The author concludes that the determination of the sedimentation speed is valuable for the diagnosis as well as for the prognosis of disturbances of the thyroid. It might also prove helpful to test the effectiveness of thyroid preparations.

**The rôle of the thyroid and parathyroid glands in vasomotor reflexes.** Vincent, S. and J. H. Thompson, *J. Physiol.* 66: 449. 1928.

Cats were thyroparathyroidectomized at least an hour after decerebration. Vasomotor reflexes were recorded before and after the second operation, with no change until about an hour had elapsed, which is regarded as a critical period because of the death at this time of many animals without any preliminary signs. In those subjects that survived the critical period, normal depressor reflex responses were changed to pressor, while normal pressor responses were augmented. This reversal was progressive until a maximum was reached, after which a second crisis occurred, usually about six hours after parathyroidectomy. Characteristic signs of tetany appeared and the blood clotted slowly. Visceral trauma during the maximal period preceding the second crisis induced pressor responses in contrast to the depressor effects normally occurring. Visceral denervation did not affect this response. Calcium salts failed to abolish the vasomotor reversal but parathyroid extract did so. Adrenalectomy simultaneous with thyroparathyroidectomy prevented reversal. When performed later the reversal responses were less marked but not prevented. When decerebration was done after thyroparathyroidectomy but before the onset of tetany, vasomotor responses were irregular, with pressor effects predominating. Death occurred much earlier. It is concluded that the augmented pressor response is due not to depression of vasomotor reflexes but to the liberation of an autocoid in some way related to the adrenals, which is normally inhibited by the parathyroid.—C. I. R.

**Heart murmurs and the subfebrile state as common thyrogenic symptoms** (*Ueber Herzgerausche und Subfebrilität als häufig verkannte thyreogene symptome*). Zollikofer, R., *Schweiz. med. Wchnschr.* 26: 674. 1929.

Heart murmurs are not necessarily indicative of heart disease. In goiter regions heart murmurs occur more often in goitrous than in goiter-free individuals. Many persons with apparently normal thyroids nevertheless possess structural and functional thyroid changes, thus explaining the incidence of heart murmurs. Goitrous children and the aged are relatively free of heart symptoms. Differentiation between primary heart murmurs and those depending upon thyroid enlargement is essential because of differences in prognosis and treatment. The prognosis in murmurs dependent upon goiter is much more favorable as this condition need not be a deterrent to complete social and economic usefulness. To refuse these persons life insurance may lead to a hypochondriac state. Occasionally, too, there is a slightly increased temperature in these patients. Particular care must be exercised to determine the presence of infectious foci and to differentiate between hyperthyroidism and tuberculosis.—I. B.

# ENDOCRINOLOGY

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### OVARIAN HORMONE EFFECTS IN OVARECTOMIZED MONKEYS

D. C. ROBERTSON, W. P. MADDUX AND E. ALLEN

Department of Anatomy, University of Missouri<sup>1</sup>  
COLUMBIA

In earlier experiments reported from this laboratory effects of ovarian and placental extracts<sup>2</sup> upon adult and immature monkeys have been described (Allen, 1, 2, 3). This work has demonstrated first, that the reddening and swelling of the "sexnal skin" and also the growth which normally occurs in the genital organs and mammary glands during the first half of the menstrual cycle may be induced by administration of this hormone and, second, that experimental menstrual periods follow cessation of injections of hormone in a majority of ovariectomized monkeys.

In the above experiments, however, full pre-menstrual development of the glands of the endometrium was not obtained. Consequently it appeared that the experimental menstrual periods in these ovariectomized animals corresponded more nearly to those occurring in normal monkeys in the absence of ovulation (Van Herwerden, 4, and Corner, 5). It seemed desirable therefore to continue the experiments with increased dosages of hormone in an attempt to ascertain the extent of growth of endometrial structures possible with these extracts. One series of hormone experiments was planned in which implants of recent corpora lutea were made toward the end of a series of injections of hormone. An additional point of interest which has been followed in this work has been a determination of the glycogen content of the epithelium of the vagina and uterus during experimental menstrual cycles. Corner's work (6) provides a control on this aspect of the problem in normal monkeys.

Following the demonstration of this active principle of ovaries and placenta in the urine of pregnant women (7, 8) it was decided to make analyses of the urine of injected animals to see what percentages of the injected hormone might be recovered during the course of the experiments.

Four female monkeys which had been under observation for seven months were used in these experiments. Where possible ovariectomy was

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1. This work has been assisted by grants from the Committee for Research in Problems of Sex of the National Research Council.

2. Names such as "follicular hormone," "folliculin," "oestrous producing hormone or oestrin," "estrogen," "menformon," "aminotin" have been used for active extracts of the ovary and placenta which have been standardized by the rat test—the production of full oestrous growth in the genital organs of ovariectomized rats.

performed between the 10th and 16th days following onset of the previous menses. Following ovariectomy periods of atrophy from 66 to 104 days elapsed before the beginning of injections. Before injections were begun each animal was operated upon again, the uterus measured and one uterine tube and mammary gland removed for controls. At this time a clipping from the fimbriated end of each control tube was examined in warm Ringer's solution for motility of cilia. The nipples were cut from the control mammary glands and sectioned. The rest of the mammary glands were prepared as flat mounts for the study of the size and number of the ducts and alveoli.

There followed a period from 20 to 33 days between the second operation and the beginning of injections in which it is probable that additional retrogression occurred in the genital organs.

The animals were injected two or three times daily as nearly at twelve or at eight-hour intervals as possible. Injections were made alternately into each hind leg. Handling the monkeys was facilitated by running them from a large cage into a small trap cage.

Following ovariectomy and during the course of control periods, the extent of coloring and swelling of the "sexual skin" was noted. Changes were followed in the contents of vaginal smears—especially the proportion of leucocytes to epithelial cells and to erythrocytes and the glycogen content of the epithelial cells.

Urine was collected for periods ranging from overnight (16-hour samples) to 24 hours. A simple method of extraction of hormone outlined by Doisy was used. This consisted of a thorough shaking of the urine samples with from 3 to 10 cc. of olive oil (depending upon the amount of urine). The oil was then removed in a separatory funnel. It is realized that this was not a thorough quantitative extraction but with reasonable precautions as to standardization it was sufficiently accurate for our purposes. The hormone content was tested by injection into ovariectomized adult rats as previously described and the results expressed in rat units.

The menstrual history of the four monkeys after ovariectomy follows. Animal SR began to menstruate on the third day after the removal of the ovaries, the duration of operative menses being three days. Animal SRS began to menstruate on the fifth day following ovariectomy; the duration of menses was two days. Animals SB and SLS did not experience operative menses. These results may be added to a similar series previously reported (9).

Following ovariectomy the reddening and swelling of the "sexual skin" decreased and slowly disappeared and leucocytes entered the masses of cells in the vaginal lumen.

Several types of extracts<sup>3</sup> were injected. One was a lipoid extract of human placenta dissolved in olive oil. A second (Amniotin, Squibb) was

3. We wish to acknowledge the generous cooperation of Doctor A. W. Lescohier of Parke Davis Company and Doctor John F. Anderson of E. R. Squibb & Sons in furnishing these extracts.

a water preparation containing 10 rat units per cc. A third (Estrogen, Parke Davis) was a water preparation containing 25 rat units per cc. A fourth (Lipo-lutein, Parke Davis) was a lipid extract of corpus luteum prepared by similar extraction methods but not standardized by biological assay. In addition to these extracts implants of fresh corpora lutea from human subjects who had ovulated recently were implanted toward the end of the experiment in two animals. These corpora lutea<sup>4</sup> were removed between the 15th and 24th days of the menstrual cycle and consequently contained considerable amounts of active material (Allen, Pratt, Newell and Bland, 10).

Animal SR was ovariectomized on July 24th. Injections were begun on October 19th, 86 days after ovariectomy. A total of 447 rat units of lipid extract of human placenta in oil solution was injected over a period of 48 days. Dosage began with 1.5 rat units per day and was gradually increased to a maximum of 25 rat units per day on the last day of injections. The animal was killed the day following the last injection and the genital organs examined histologically.

Toward the end of the first week of injections the colorless "sexual skin" of the ovariectomized animal reddened and then gradually deepened until a maximum redness was obtained by the end of the experiment. There was no swelling of the skin of these regions. Leucocytes were completely absent from the vaginal smears after the first two weeks of injections and the number of cornified cells increased rapidly. Since the animal was killed the day following the last injection, too soon for the occurrence of menses, the experiment deals only with the anabolic phase of the menstrual cycle.

The above experiment was designed to imitate conditions which sometimes exist in normal animals where periods of two or three months of amenorrhea may occur (1). That the ovaries of such animals are actively secreting this hormone is shown by the reddening of the "sexual skin." The ovaries in such cases usually have several follicles (occasionally one or two cystic ones) but no corpora lutea. In the above experiment therefore it is interesting that no menstruation occurred during continuous hormone stimulation sustained for forty-eight days.

A second series of injections were made into three animals, SLS, SB and SRS, beginning on November 5th. Before beginning injections and after periods of from 83 to 91 days following double ovariectomy the animals were opened, uteri measured and one tube and one mammary gland removed from each for controls. Control smears were taken of the vaginal contents. Control measurements of the uterus are listed in table I and the conditions of the tubes and mammary glands will be discussed under histological findings. In the vaginal smears of the controls considerable numbers of leucocytes were present (Fig. 1) and it was not possible to demon-

4. These corpora lutea were enucleated from ovaries at operations by Doctor J. P. Pratt of the Henry Ford Hospital, Detroit, and Doctor Q. T. Newell of Barnes Hospital and Washington University, St. Louis.



strate the presence of glycogen in the epithelial cells. The period of injections lasted from 24 to 27 days. For the first 13 days two injections were given at 12-hour intervals. During the remainder of the experiment three injections a day were made at approximately eight-hour intervals. A total of 886 rat units was injected into animal SLS, 981 rat units into animals SB, and 882 rat units into animal SRS.

In animals SLS and SRS one-half of a human corpus luteum was implanted on the 22nd, 23rd and 24th days of injections. The human corpora used were cut into small pieces to facilitate absorption of any hormone specific for the corpus luteum which might be already present in them. In animal SB from the 22nd to 27th days injections of "lipo-lutein," a

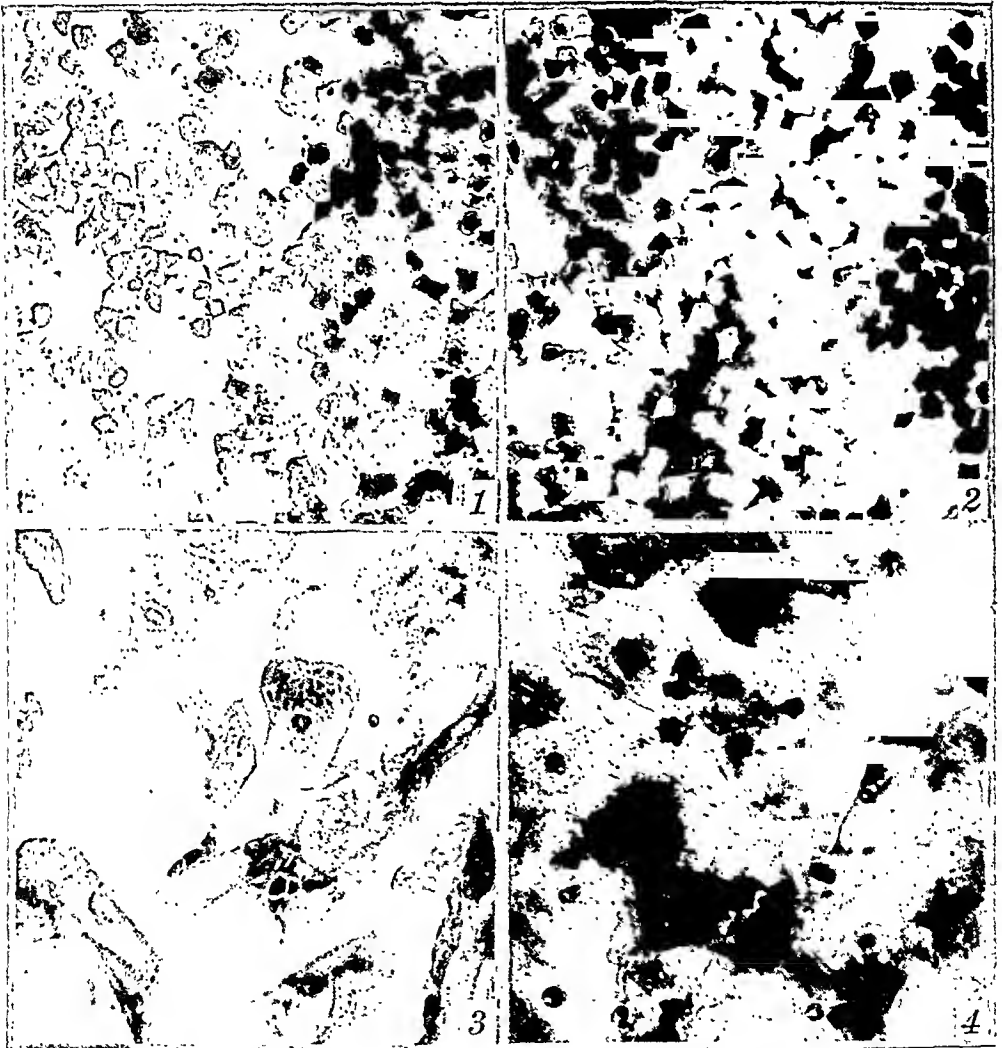


Fig. 1. Cells from the vaginal lumen of an ovariectomized control monkey. Partly cornified epithelial cells with pycnotic nuclei and varying numbers of leucocytes. X 50.

Fig. 2. Cornified epithelial cells from the vaginal smear toward the end of a series of injections. Leucocytes are absent. X 50.

Fig. 3. Glycogen granules in epithelial cells from vaginal smear of monkey SLS toward the end of a series of injections of hormone. X 294.

Fig. 4. Cells of vaginal smear of monkey SRS during an experimental menstrual period. Nucleated epithelial cells, a few leucocytes and erythrocytes. X 220.

lipoidal extract of corpus luteum, were administered. This corpus luteum implant and extract were administered at the same time that the follicular hormone was being given because it has been demonstrated that the human corpus luteum during the last half of the menstrual cycle contains large amounts of this hormone (10) as well as other active substances possibly specific for the corpus luteum (11, 12, 13).

By the end of the first week of injections reddening of the "sexual skin" appeared. This deepened by the end of the second week and before the end of the period of injections was reached had attained a maximum coloration. In animal SLS an extreme amount of swelling of this skin occurred. In the other two animals the swelling was not so marked.

The leucocytes disappeared from the smear by the middle of the second week of injections. Toward the latter half of the experiment large amounts of mucus appeared in the vaginal contents. There was a marked increase in the number and in cornification of the epithelial cells (Fig. 2). During the last week of injections glycogen could be demonstrated in the epithelial cells of the smear (Fig 3).

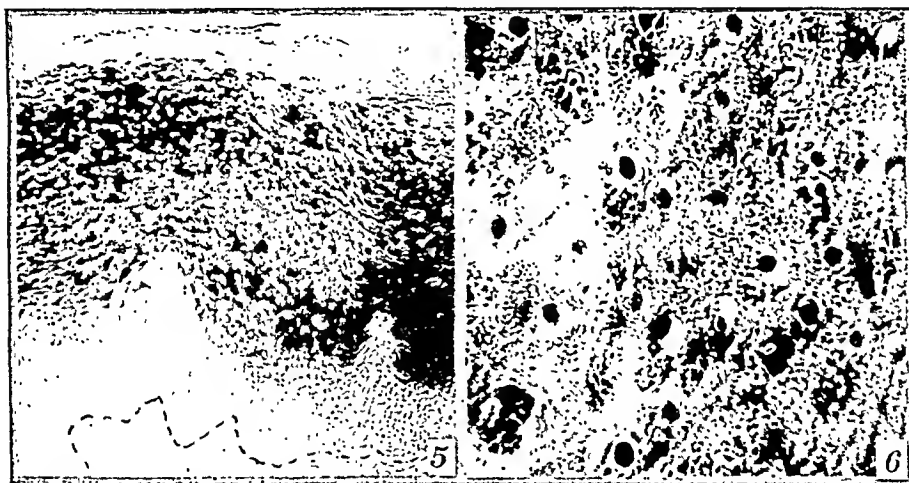


Fig. 5. Vaginal wall of animal Slt toward the end of a series of injections. This section was stained with Lugol's iodine for a demonstration of glycogen. The dotted line indicates the germinal layers of the epithelium. It will be noted that most of the glycogen is in the outer degenerating cells. X 75.

Fig. 6. A small section of the vaginal wall of monkey SLS stained with Best's carmine to show glycogen content of epithelial cells. X 440.

Animal SLS was killed on the last day of injections, too soon after cessation of injections to permit the appearance of menses. Animal SB was killed on the third day following the last injection. Although no menses were visible externally, when the genital tract was removed and opened an early menstrual condition was found, the lumen of the uterus and inner part of the vagina being filled with menstrual material. Animal SRS was killed on the second day following the last injection. At this time menses were apparent externally and this condition was checked by smears (Fig. 4) and by gross and histological examination.

A gross examination of the genital organs of these three monkeys at autopsy showed the following points. A thick, white accumulation of material was found in the vaginal lumen. This was composed of sloughed epithelial cells and mucous discharged from the cervical glands. In addition, in the two animals already noted the endometrium was hemorrhagic and menstrual discharge was present. The endometrium of animal SB, killed on the first day after the last injection, was a pale white color.

In the three animals of the last series measurements were taken of the uterus at the time of ovariectomy, at a control operation before injections were begun and again at the end of the series of injections. These measurements are included in Table I. These figures show a considerable decrease in size due to castration atrophy but a complete recovery to equal or exceed the size of the normal uterus following injections.

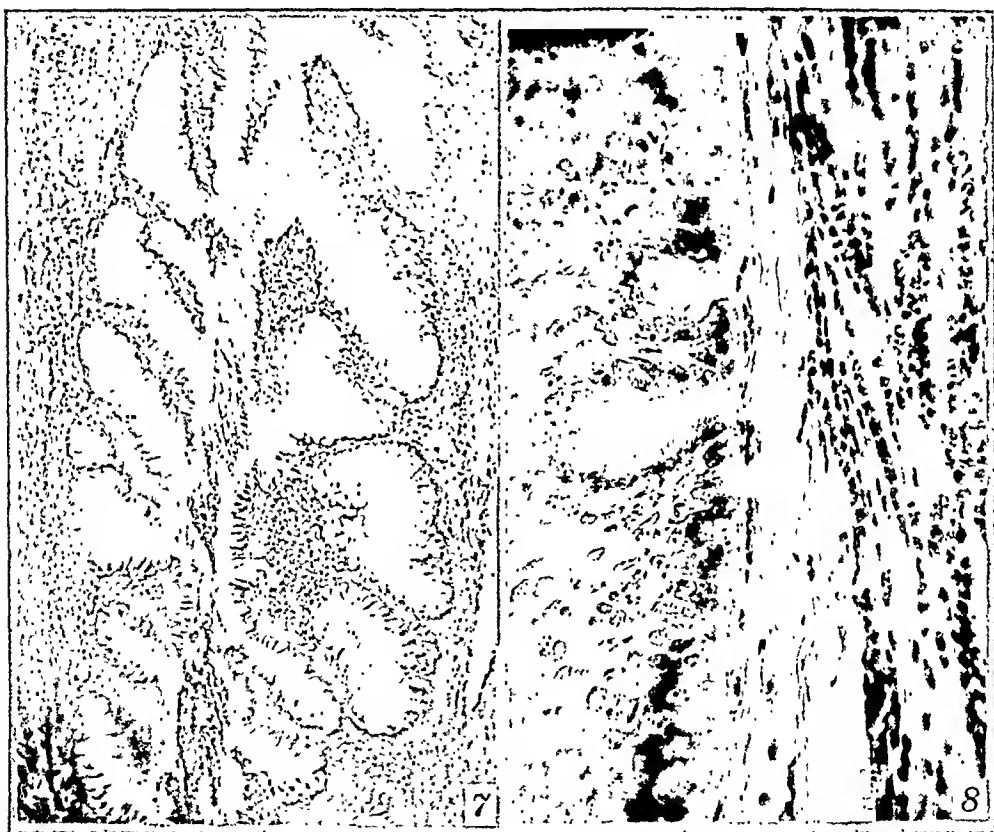


Fig. 7. A section of a gland from the external os of the cervix in a hypertrophied condition at the end of a series of injections. X 44.

Fig. 8. A higher magnification from the same gland showing a high columnar epithelium and many leucocytes in the stroma, in the epithelium and in the gland lumen. X 200.

Histologic sections of the vaginal wall confirmed conclusions drawn from earlier experiments as to extremely rapid growth of the epithelium (1). The extreme thickness to which the vaginal wall can be developed, especially when compared to the control condition after castration atrophy, is surprising.

The presence of glycogen was demonstrated in sections of the vaginal wall from all three animals of the last series (Figs. 5 and 6). It was scarce, if present at all, in the vaginal epithelium of the control animal.

In the animals in which a day or two elapsed between the last injection and death of the animal, leucocytic infiltration of the lower layers of the epithelium had begun.

TABLE I  
TABLE OF UTERINE MEASUREMENTS

Time of Measurement	Monkey		
	SRS	SB	SLS
At ovariectomy.....	12 x 8 mm.	13 x 10 mm.	9 x 7.5 mm.
Just before injections (Atrophy 66-101 days) . . .	10 x 5.6 mm.	11 x 5.6 mm.	9 x 5.3 mm.
At end of injections.....	12 x 9 mm.	12 x 5.6 mm.	15.5 x 9 mm.

The cervixes of the injected animals were considerably hypertrophied. The glands near the external os were tremendously enlarged and coiled (Fig. 7). The epithelium was high columnar. Secretion by these glands was active as shown by secretion droplets along the free borders of the



Fig. 9. A section of the uterus of monkey SLS killed on the last day of injections. This is a typical interval type of endometrium. Hyperplasia in the gland epithelium is at its height. X 50.

Fig. 10. Higher magnification of one of the glands in the same endometrium stained with Best's carmalum to show glycogen granules in the glandular epithelium and lumen. X 298.

cells. The stroma surrounding the glands was heavily infiltrated with leucocytes and many of these could be traced into the lumen of the gland (Fig. 8). A few small glycogen granules were also present. This leucocytic infiltration in the cervical glands under the influence of ovarian hormone is as yet unexplained. It has been present in all of our monkeys

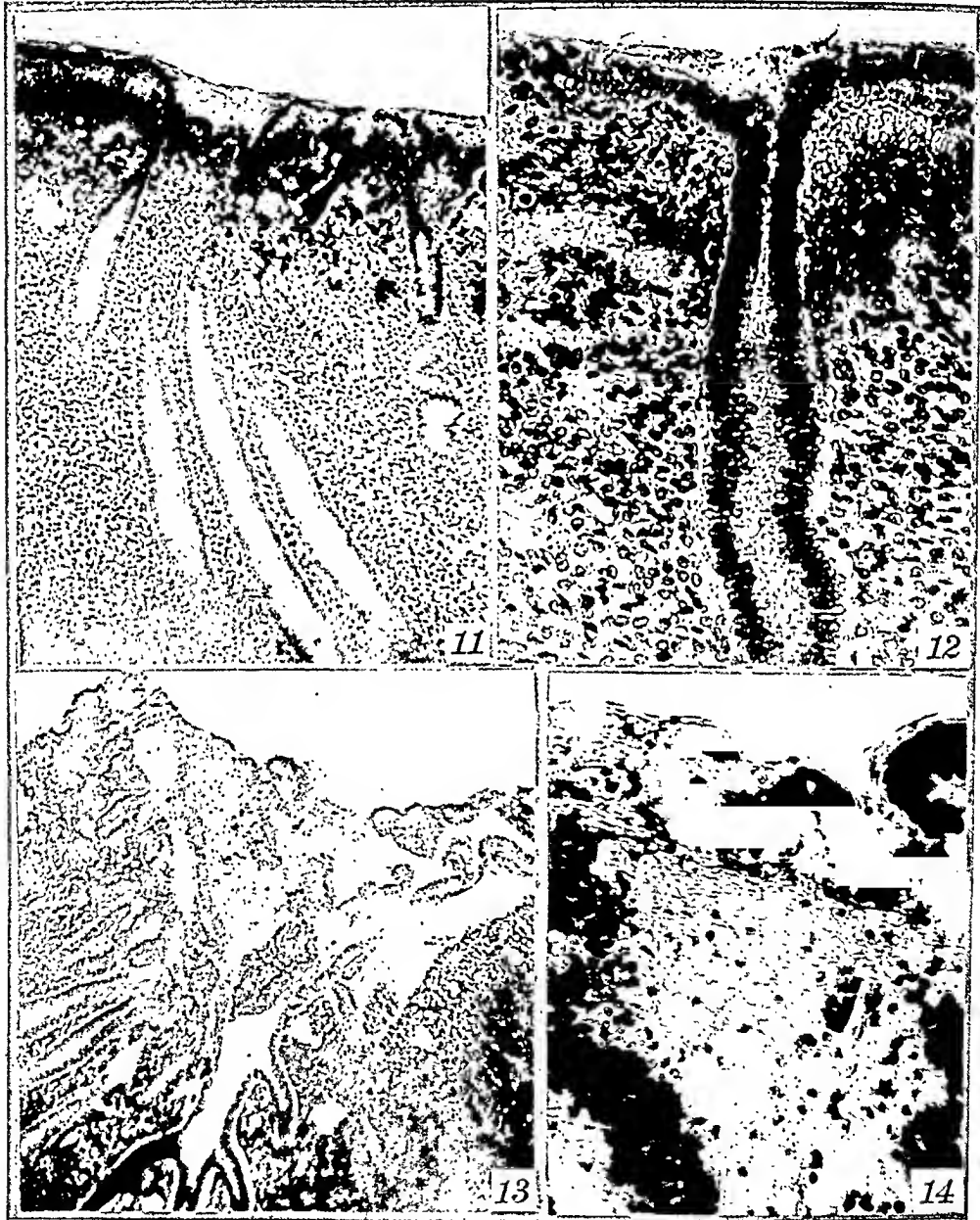


Fig. 11. Section of endometrium of animal SB, killed on the third day after the last injection. The glands had not reached typical premenstrual development. The sub-epithelial stroma was edematous and extravasation of blood had begun. X 50.  
 Fig. 12. Higher magnification of endometrium from the same animal showing the sub-epithelial hematoma. X 220.  
 Fig. 13. Section of endometrium from animal SRS on the second day after the last injection. This was a later menstrual stage in which the superficial layer was being sloughed. X 40.  
 Fig. 14. Higher magnification of the menstrual material in the lumen of the uterus showing pieces of glands, erythrocytes and polymorphonuclear leucocytes. X 133.  
 Sections of the uterine tubes from control and injected animals.

under hormone stimulation. The question arises if this may be a physiological leucorrhea.

For comparison with the uteri from injected animals there was one control uterus from monkey SB removed after a period of 66 days of castration atrophy. This uterus was small (12x7 mm.) and anemic. The

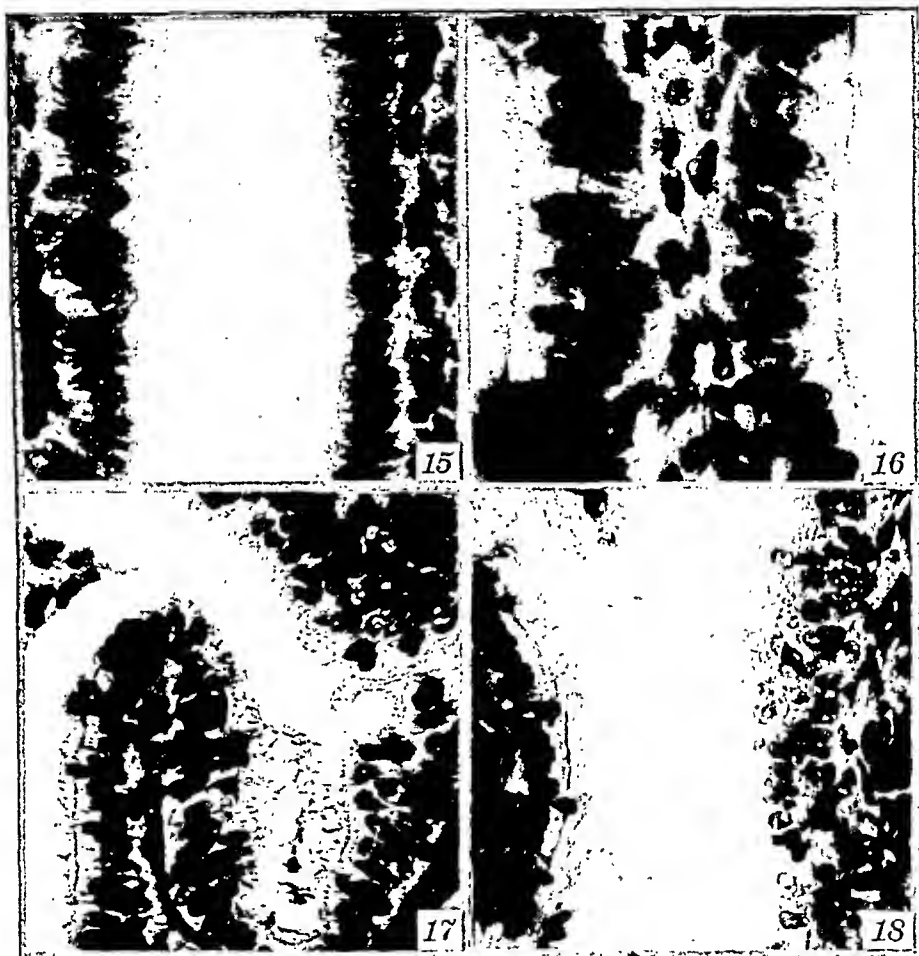


Fig. 15. Non-elliated epithelium from control tube of animal SB, 54 days after ovariectomy. X 710.

Fig. 16. Epithelium from the other tube of the same animal at the end of injections. Note high columnar structure and regeneration of cilia. X 710.

Fig. 17. Tubal epithelium of animal SB at the end of injections. X 330.

Fig. 18. Another section of epithelium from the same tube. X 330.

endometrium was thin and compact. The surface epithelium was degenerate and contained no mitotic figures. The glands were few and poorly developed. Glycogen was present in the epithelial cells of the glands in traces only.

Of the four uteri removed following injections, two (from animals SB and SLS) had endometrium of the interval type as far as gland devel-

opment was concerned (Fig. 9). The superficial stroma was very loose meshed and edematous. Many mitotic figures were present in the superficial epithelium and glands. Secretion globules were present in the gland lumina and along the outer borders of the cells. Glycogen granules were very abundant in both the cells of the glands (Fig. 10) and the superficial epithelium. It is probable that the corpus luteum extract and implants were not continued for a period sufficient to carry gland development beyond the interval stage because Corner and W. Allen (12) and Hisaw (13) have reported pseudo-pregnant and premenstrual conditions of uterine glands in the rabbit and monkey, respectively, due to corpus luteum extract.

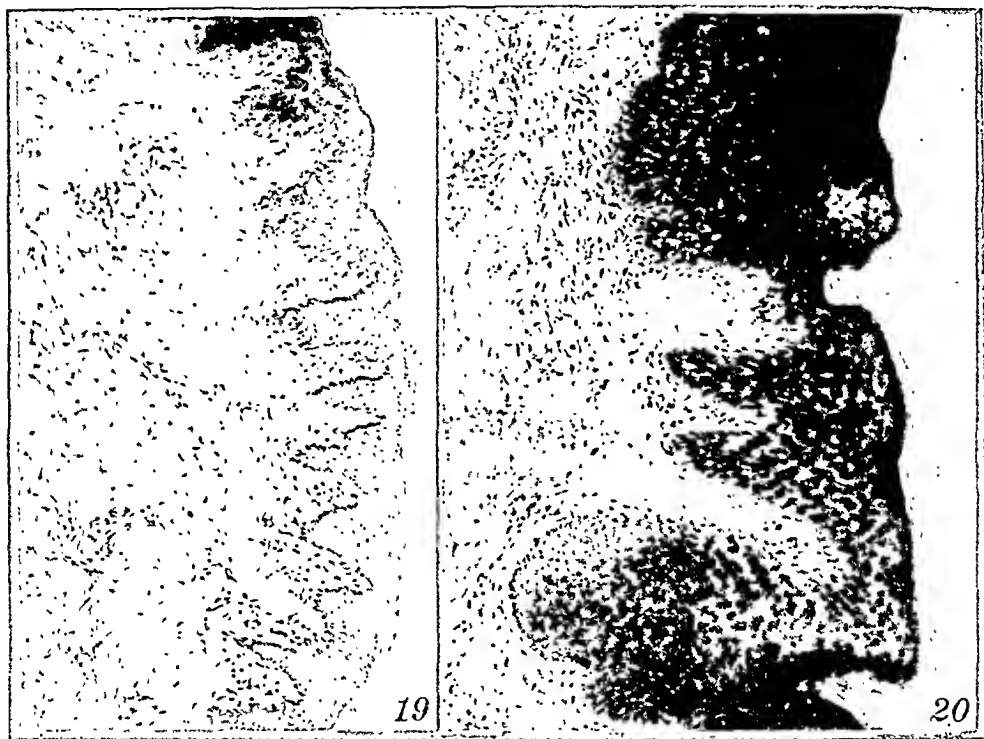


Fig. 19. Section of epithelium of the nipple from control gland of animal SRS 53 days after double ovariectomy. X 100.

Fig. 20. Epithelium from the other gland of the same animal at the end of a period of injections. X 100.

The other two uteri (from animals SRS and SB) were in a typical early menstrual condition. The endometrium was thicker than the control; the glands as would be expected at an early menstrual stage were not very well developed. Sheets of superficial epithelium and adjacent stroma had been loosened and cast off and menstrual blood was present both under the epithelium and in the lumen of the uterus (Figs. 11, 12, 13 and 14). The incidence of mitosis was not high and only small amounts of glycogen could be demonstrated in the epithelial cells.

The epithelium of the left uterine tubes which were removed for control specimens was relatively low and cilia were few or absent (Fig. 15).

Motility of cilia could not be demonstrated in small pieces of the fimbriated ends examined in warm Ringer's solution. Small round cells were scattered abundantly throughout the epithelium close to the basement membrane. Only small amounts of glycogen were demonstrable.

The epithelium of the right uterine tubes removed after injections was in marked contrast to that of the controls. It was higher and better ciliated (Figs. 16, 17 and 18). Motile cilia were observed in fresh preparations. The small round cells next to the basal membrane were much more scarce than in the control tubes. A high incidence of mitoses was indicated and glycogen granules were fairly abundant in the epithelial cells. A remarkable recovery from atrophy following ovariectomy was apparent.

In studying injection effects on the mammary glands the left gland from each animal was used for a control and the right for an experimental specimen. The epidermis of the nipples of the control glands was not very thick, being composed of from three to twelve layers of nuclei (Fig. 19). It was difficult to identify mitoses. The epithelium of the nipples after injections was much thicker; there were 27 layers of nuclei in the thickest specimen and with a thick stratum corneum in addition (Fig. 20). Mitoses were abundant in the germinal layers.

The mammary glands after injections were considerably larger than the controls; the ducts longer, larger and more branched and having more alveoli. This phase of the work is well illustrated in an earlier publication (1).

The condition of the luteal tissue which was placed in subcutaneous pockets in these monkeys was interesting. This tissue was heavily infiltrated with leucocytes and for the most part not recognizable as luteal tissue. In two implants, however, which had been in the hosts four and six days, respectively, small areas of apparently normal luteal tissue could still be identified.

A total of nineteen samples of urine was analyzed from monkeys SB, SLS and SRS during the course of injections. During the collection of the samples injections were made three times daily at approximately eight-hour intervals, the daily dose ranging from 18 to 58 rat units. Analyses of nine samples from spayed animals before injections were made for controls and in none was enough hormone obtained to give a positive rat test. The amount of hormone recovered from the urine of injected animals ranged from 12.9 to 57 per cent of the hormone injected, the average being 29.3 per cent.

#### SUMMARY

Ovarian hormones were injected into four ovariectomized adult female monkeys. In two corpora lutea also were implanted. Two experimental menstrual periods followed cessation of injections of oestrous-producing ovarian hormone. Sections of the uteri showed typical menstrual endo-



metria of the non-ovulating type. Three implants of recent human corpora lutea did not increase the growth of the endometrial glands beyond the interval stage.

Toward the end of the series of injections it was possible to demonstrate the presence of considerable amounts of glycogen in the epithelial tissue of the uterus and vagina. Glycogen was relatively scarce in the control tissues. Glycogen could also be demonstrated in the epithelial cells sloughed from the vaginal wall. In the vagina it increased in amount as cornification of epithelial cells progressed.

The epithelial lining of the uterine tubes of the injected animals showed remarkable recovery from atrophy following ovariectomy. Mitotic division of cells and regeneration of cilia in some regions were demonstrated. Extensive growth was also induced in the mammary glands, including the skin of the nipples.

Considerable amounts of the hormone injected were recovered from the urine of experimental animals.

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# ANTERIOR LOBE PITUITARY SUBSTANCE AND BASAL RESPIRATORY METABOLISM

MILTON O. LEE AND JULES GAGNON

The Memorial Foundation for Neuro-Endocrine Research,  
Harvard Medical School  
BOSTON, MASS.

Despite a considerable amount of negative and very little positive evidence as to the efficacy of anterior lobe substance when administered by the alimentary tract, such therapy is nevertheless extensively used. The most of the carefully controlled experimental work (1, 2, 3, 4, 5) on feeding this material to dogs, cats, rats and mice has shown it to be entirely without effect on general bodily or genital growth and development. The few positive results on mammals that have been reported are largely equivocal and have been derived from poorly controlled experiments on an insufficient number of animals. Reports both of stimulation and inhibition of growth and development have been made. Patterson (6) in a recent paper has summarized this experimental work.

Clinically, anterior lobe substance by mouth has been used in cases diagnosed as "hypopituitarism," "hypo-anterior lobe," "hypogenitalism" and "infantilism," in cases of obesity, amenorrhea, and of disturbed metabolism which are supposedly not due to thyroid disorders. For the most part only the positive results of such therapy have been reported, but those show a still poorer case for its efficacy, in that the cases have usually been entirely uncontrolled, the anterior lobe preparation has often been used in connection with thyroid or other opotherapy, and the criteria of the results are very superficial.

We have found that extracts of the anterior lobe containing the growth promoting principle when injected parenterally cause a definite lowering of the basal gaseous metabolic rate, both in giant rats (7) and in rats before a condition of gigantism has had time to develop (unpublished work). McCordock (8) has recently reported that the oral administration of desiccated anterior lobe substance to guinea pigs caused a depression in the activity of the thyroid, with a marked lowering of the number of mitoses, the production of only medium sized or small acini with hard colloid compressing the lining epithelium into thin strands. We have observed that in rats injected with the growth promoting principle for some time, the thyroids are grossly smaller in size. It would seem that if anterior lobe substance is at all potent when given by mouth, some effect upon the respiratory metabolism should be produced.

## EXPERIMENTAL

Fourteen male albino rats of a pure Wistar strain and approximately six months old at the beginning of the experiment were used. After a

preliminary period of about three weeks, during which at least two satisfactory basal metabolic rate determinations were made for each animal, 8 of the rats were given desiccated anterior lobe substance\* for 62 days. This was given each morning, mixed with a little bread and milk, to each rat individually. No difficulty was experienced in getting the animals to eat the mixture. The dosages used were 2 grains of desiccated gland substance per day per rat for 8 days, then 4 grains for 8 days and finally 8 grains per day per rat for 46 days. One grain of the desiccated gland corresponds to about 5 grains of fresh anterior lobe. Each rat at the end of the feeding period had received a total of 370 grains or 24 grams of the dried substance, which might correspond to a relative amount of at least three or four pounds in man. During the feeding period and for several months afterwards frequent basal metabolic rate determinations were made for these rats and for the controls. One of the rats receiving anterior lobe and two of the controls were killed accidentally before the completion of the experiment.

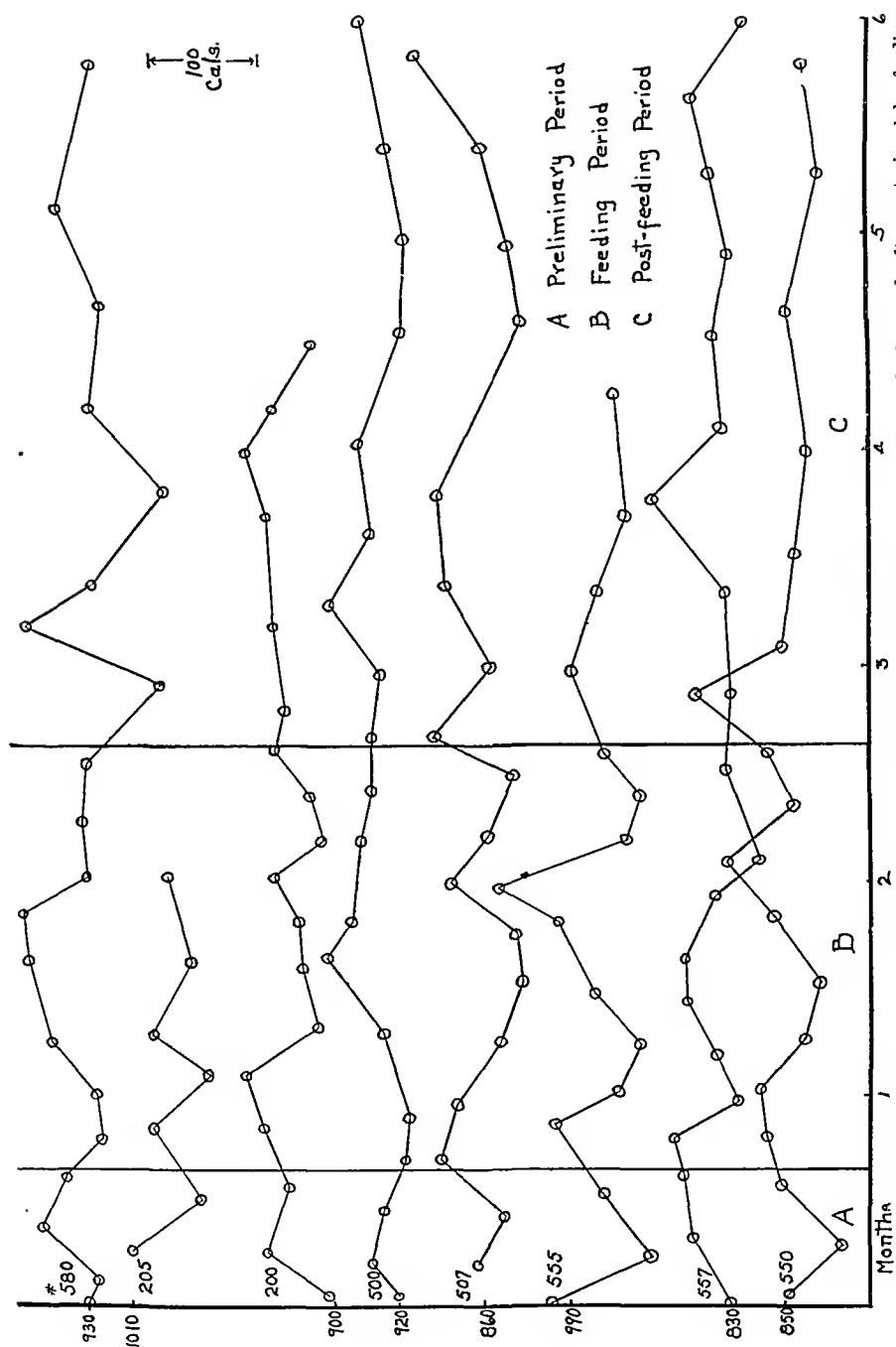
The basal metabolic rate determinations were made by a closed circuit, oxygen consumption method using a four unit apparatus and a technic that has been carefully standardized. Each determination used in the calculations represents the lowest rate measured in several tests over a four to six hour period and 18 to 24 hours after the last ingestion of food. All determinations used were considered satisfactory from a technical standpoint, that is, the starved animals had shown few or no movements during the test, there was no leak in the system and the soda lime tubes showed proper absorption. The metabolic rates are expressed in terms of calories per day per square meter of body surface, which was calculated from the formula

$$S=10.76 W^{0.61} \left( \frac{0.31}{\frac{W^{1/2}}{L}} \right)$$

in which  $W$  is body weight in grams and  $L$  body length in centimeters.

Table I gives a summary of the results. The average metabolic rate for the 8 experimental animals during the preliminary period was 909 calories per day per square meter. Omitting the data for rat 205, which died before the completion of the experiment, the average rate was 900 calories. During this period the four control rats which lived throughout the experiment had an average rate of 891 calories. During the feeding period the experimental rats showed an average metabolic rate of 913 calories, or without No. 205, of 905 calories. The controls during this period had an average rate of 897 calories. During the post-feeding period the 7 rats fed anterior lobe had an average rate of 901 calories and the controls of 900 calories. Figure 1 shows graphically the course of the metabolic rate in each rat.

\*Burroughs-Wellcome and Parke Davis Company desiccated anterior lobe pituitary substance was used.



Month

Fig. 1. Basal metabolic rates of individual rats, in calories per square meter, before, during and after anterior lobe feeding.

The small differences in the metabolic levels, as given by the averages, are entirely insignificant, and the fluctuations shown in the individual graphs occur equally in control rats. No differential effect of the three dosages is apparent. Respiratory quotients determined at frequent intervals showed no significant deviations from the normal value of approxi-

TABLE I

BASAL METABOLIC RATES BEFORE, DURING AND AFTER ANTERIOR LOBE FEEDING

Rat No.	Preliminary Period			Feeding Period			Post-Feeding Period		
	Weight Range Gms.	No. of Tests	Cals., Day, Sq. M. Average	Weight Range Gms.	No. of Tests	Cals., Day, Sq. M. Average	Weight Range Gms.	No. of Tests	Cals., Day Sq. M. Average
200	296-300	3	936	292-310	9	937	308-316	5	947
205	332-335	2	975	338-353	5	966	.....	..	...
500	322-326	3	932	322-340	7	941	320-342	9	936
507	269-278	2	851	265-294	8	856	280-295	7	873
550	274-276	3	830	278-300	8	851	290-309	7	850
555	257-260	3	949	280-301	9	957	295-309	4	947
557	262-265	3	856	262-270	8	846	270-295	9	844
580	275-278	4	946	282-320	8	945	317-341	8	912

mately 0.72 either during or after the feeding period. While it is true that negative results are not definitely conclusive, it would appear that the preparations of anterior lobe and the dosages used in this work are entirely ineffective in altering the level of metabolic activity.

#### SUMMARY

Desiccated anterior lobe pituitary substance fed to 8 adult rats in doses of 2, 4 and 8 grains per day per rat for 62 days had no effect on the basal respiratory metabolism or on the respiratory quotient.

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# THE RÔLE OF THE ADRENAL MEDULLA IN THE MAINTENANCE OF BLOOD PRESSURE

SWALE VINCENT AND J. H. THOMPSON

From the Dept. of Physiology, Middlesex Hospital, Medical School  
LONDON

## LITERATURE

Some of the earlier workers investigating the function of the adrenal medulla concluded as a result of their experiments that a constant secretion of adrenaline occurs which helps to maintain the normal blood pressure.

Strehl and Weiss (9), who extirpated the adrenal gland on one side in rabbits, found that when the adrenal vein of the other side was clamped the blood pressure immediately fell, and that there was a recovery when the clamps were released. Marked falls of blood pressure were obtained in this way.

Young and Lehmann (16) working in Vincent's laboratory repeated the experiments upon dogs but found little, if any, fall of blood pressure.

One of the first workers to grow suspicious on this point was Vincent, who was unable to obtain any lowering of blood pressure when the adrenal veins were clamped and a consequent recovery when the clamps were released.

Hoskins and McClure (6) using dogs under various anaesthetics obtained only transitory variations of blood pressure after ligature of the adrenal veins.

Much evidence has been advanced by various workers to militate against the theory that the adrenal medulla is a factor in the maintenance of blood pressure. Moore and Purinton (7) showed that small amounts of adrenaline, such as presumably are liberated normally from the adrenal glands, cause a lowering of the blood pressure. Stewart and Rogoff (8) found that in animals from which one adrenal gland was removed and the secretory fibres from the semi-lunar ganglia on the other side transected, no ill effects were apparent.

More recently, Cannon (3) using the denervated heart preparation has demonstrated the secretion of considerable quantities of adrenaline in the medulla in conditions of stress, and has established the well-known "emergency" theory. Previous investigations by the same worker failed to reveal any adrenaline present in the blood collected from the vena cava and subjected to various physiological tests.

Cramer (4), however, has shown that subjection of an animal to cold for a prolonged period results in exhaustion of the adrenal medulla, and Vincent (11) has demonstrated the same effect after fatigue in rats.

Moreover, the low blood pressure always present in Addison's disease remains to be explained. In this disease the basal metabolic rate is very considerably lowered, and it is significant that in animals after complete adrenalectomy the metabolic rate is reduced by about 25 per cent, and can be raised again to the normal by the injection of adrenaline.

An important contribution to this subject has been made by Bazett (2). Using cats chiefly, this worker attempted to measure the rate of the fall of blood pressure in animals in which the adrenals were removed under ether anaesthesia, under urethane anaesthesia, and in decerebrate animals. All experiments were carefully controlled. Excision of the adrenal glands in the decerebrate animal led to death in about six hours, the pressure beginning to fall about one hour after excision. Control animals showed no falls of blood pressure 28 hours later. Decerebrate preparations developed these changes more quickly than animals anaesthetised. Moreover, animals anaesthetised and allowed to recover failed to manifest such fall of blood pressure. A similar series of results have been obtained recently by Vincent and Thompson (14).

#### ANATOMICAL CONSIDERATIONS

Cow (5) has indicated the presence of a collateral circulation in the region of the adrenal gland. Vincent and Wright (15) suggested that the persistence of the "dip" in the splanchnic curve after stimulation of the splanchnic nerve under chloralose anaesthesia with the adrenal veins tied, was due to a collateral circulation. Thompson (10) confirmed this, and Vincent and Thompson (13) showed that the effect was exaggerated by chloralose due to the fact that this drug activates the secretion of adrenaline and possibly forms a weak chemical compound more stable than adrenaline; and which sensitises nerve terminals.

Recently Vincent and Thompson (14) have demonstrated in detail the anatomical arrangements of this collateral circulation, which in brief consists of one or more small veins draining the adrenal veins in its course across the gland, into the renal vein, and also a more complicated plexiform group of vessels situated posteriorly.

Therefore, the older experiments in which only the adrenal veins were clamped or ligatured were fallacious, since the adrenaline could still leak through the collateral circulation.

#### METHODS AND RESULTS

The present series of experiments have been undertaken in order to re-investigate this problem in the light of the new anatomical facts. The experiments have been performed upon cats under various kinds of anaesthetics, and in the decerebrate condition. Anaesthetics used include ether, chloroform, chloralose, luminal sodium, urethane, and different combinations. In all cases the results were identical and the presence or absence of anaesthetic is immaterial to the actual result, although, as will be dem-

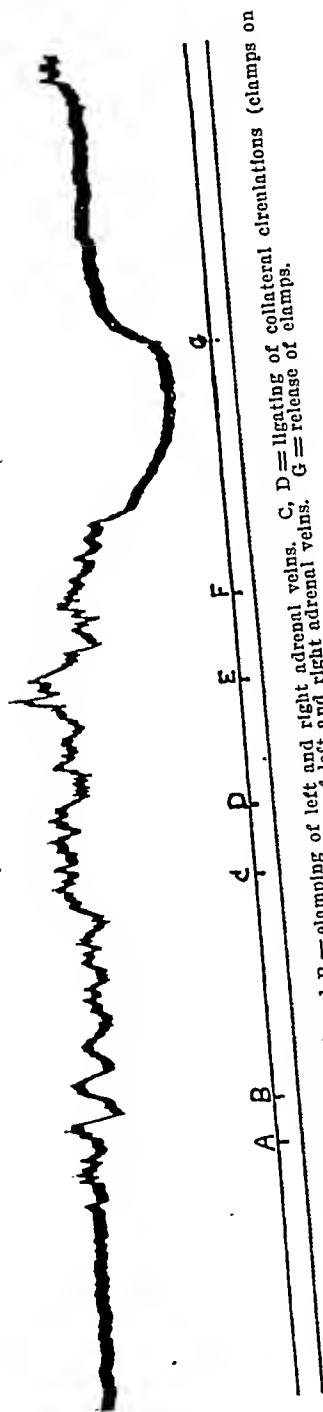


FIG. 1. Cat. Ether anaesthesia. A and B = clamping of left and right adrenal veins. C, D = ligating of collateral circulations (clamps on veins having been removed between B and C). E, F = clamping of left and right adrenal veins. G = release of clamps.

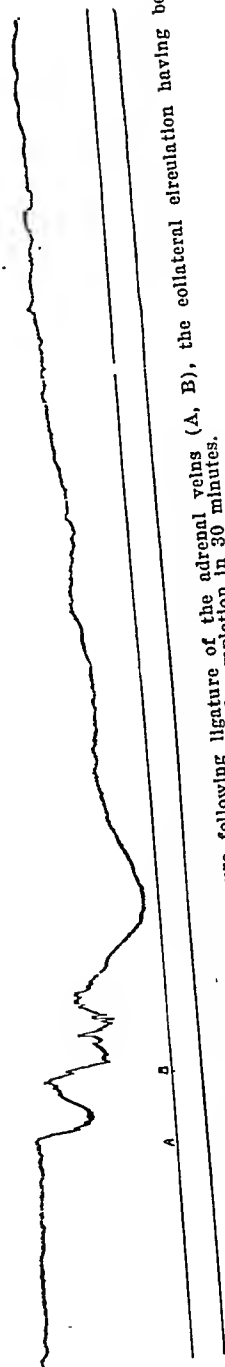


FIG. 2. Cat. Decerebrate. Fall of blood pressure following ligation of the adrenal veins (A, B), the collateral circulation having been previously ligatured. Note the gradual recovery process which reached completion in 30 minutes.



onstrated later, the presence of some anaesthetics is liable to introduce a fallacy due to a masking effect.

The methods employed in this long series of experiments are briefly as follows: The usual blood pressure record from the carotid artery was taken, and nothing done until the blood pressure maintained a constant level for at least a period of twenty minutes. The skin incision was then made (the glands were usually removed via the abdominal route), and the effect upon the blood pressure noted. If any fall of a magnitude equivalent approximately to that which might be expected as a result of adrenalectomy occurred, the animal was discarded so far as the present work was concerned. Similar precautions were adopted after the peritoneal cavity was opened and the intestine handled.

Ligatures were then placed upon the adrenal veins (as in the older experiments) and the effect upon the blood pressure carefully observed. The usual result was a transient fall of blood pressure. Recovery was rapid and the blood pressure remained at its original level. (Fig. 1. A, B.) This confirms the experiments done by this method. We have noticed that if during this procedure undue manipulation takes place small rises of blood pressure occur, presumably due to expression of adrenaline from the gland. In other experiments instead of ligating the adrenal veins, the collateral circulation was cut off. This can be done by placing ligatures round the small vein or veins draining the adrenal vein during its course across the gland and which can easily be found, and by tying a circular ligature round the posterior part of the gland. This latter procedure is somewhat difficult and must be done with care so as to avoid damaging the post ganglionic fibres from the semi-lunar ganglia, and also to avoid kinking the adrenal vein.

No change of blood pressure occurred as a result of the procedure. (Fig. 1. C, D.)

The adrenal veins were then clamped and a marked though gradual fall of blood pressure invariably resulted. (Fig 1.) The fall was considerable, often attaining the proportion of 50 mm. Hg. A direct relationship seems to exist between the initial height of the blood pressure and the depth of the fall. The fall persisted for approximately twenty minutes and there then began a very slow recovery which continued until the original pressure was reached. (Fig. 2.) If, however, the clamps on the adrenal veins were removed prior to the return of the original pressure, a very much sharper recovery occurred; indeed, in many instances it was almost immediate. (Figs. 1, 3.)

Precisely similar results have been obtained by reversing the order of the operative procedures, that is, clamping the adrenal veins first and the collateral circulation afterwards.

Complete adrenalectomy exhibited the same phenomena—the fall of blood pressure and slow subsequent recovery. (Fig. 4.)

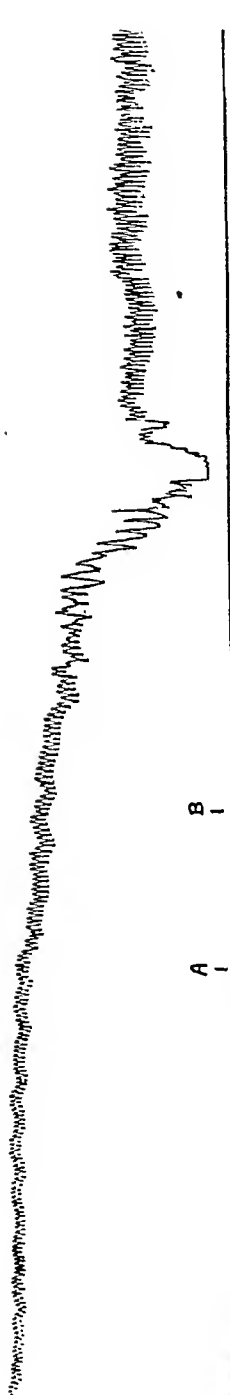


Fig. 4. Cat. Decerebrate. A = left adrenalecctomy. B = right adrenalecctomy. N.B.—There was a slow recovery comparable to that in Fig. 2 and which was completed in 20 minutes.

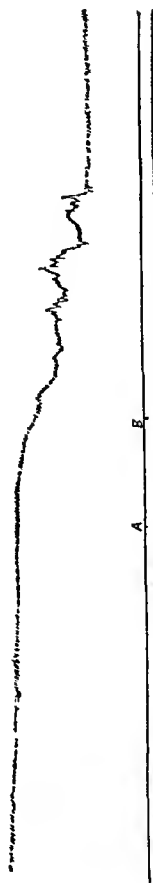


Fig. 5. Cat. Decerebrate. Both kidneys removed 20 minutes earlier; no change in blood pressure. At A, B complete adrenalecctomy performed. No recovery from the fall of blood pressure occurred and the blood pressure remained constant at the lower level for one hour, after which the animal died from respiratory failure.

That these falls of blood pressure were not due to operative procedures was fully proved in several experiments in which various organs were removed before adrenalectomy. Removal of the kidneys for instance caused no variations in mean blood pressure, but subsequent adrenalectomy resulted in the fall of pressure above described. These falls of blood pressure cannot therefore be ascribed to vaso-motor reflexes caused by the abdominal manipulation [Vincent and Thompson (12)].

A very interesting variation of the usual result was obtained when any large portion of the splanchnic area was removed prior to the experiment. For example, when 3 feet of intestine was removed the recovery process was much delayed, and was never complete. The same effects were observed when the kidneys were removed; and if a sufficient area was extirpated there was a complete failure of the recovery process and the blood pressure remained constant at a much lower level than normal.. (Fig. 5.)

As already indicated, these results have been obtained in the decerebrate preparation and in the anaesthetised animal without exception. It must be pointed out, however, that the decerebrate preparation is not suitable for this experiment because so frequently respiratory failure develops [Vincent and Thompson (14), Bazett (2)] before the recovery of the

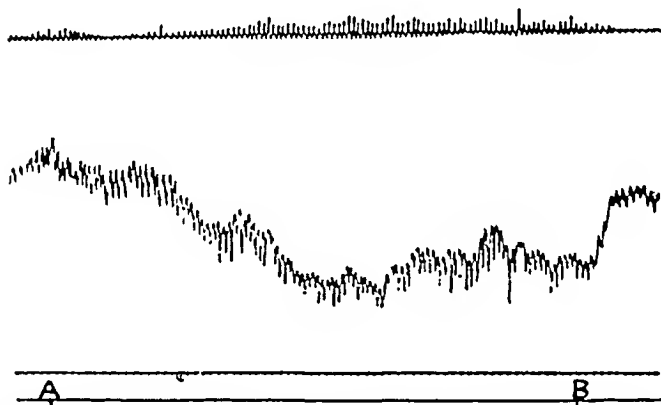


Fig. 3. Cat. Chloralose anaesthesia. Collateral circulation ligatured. Fall of blood pressure and recovery therefrom by clamping (A) and releasing clamps on (B) the adrenal veins.

blood pressure. The use of anaesthetics also possesses certain disadvantages; this especially refers to the volatile group. Variations in the depth of anaesthesia produces considerable alterations in blood pressure, thus entirely masking the result unless precautions are taken to insure a constant supply of anaesthetic, etc. For this reason chloralose and luminal sodium are most suitable.

#### DISCUSSION

Examination of the results shows that temporary depression of the blood pressure results from the elimination of the adrenal gland secretion from the circulatory system. The earlier workers failed to obtain this

result due to a leakage of adrenaline through collateral channels left open. Austmann and Halliday (1) using dogs under ether anaesthesia failed to obtain the depressor effect after adrenalectomy probably because of the difficulties associated with ether anaesthesia to which reference has already been made. It is significant to note, however, that these investigators make mention of exceptions in their series of negative results.

Our present investigations confirm much of Bazett's work (2). We have found, however, that the fall of blood pressure occurs much earlier than indicated by this work, and we believe that the recovery process is a most important factor. Apparently the vaso-motor mechanism, particularly of the splanchnic area, acts in a compensatory fashion after adrenalectomy so that in a short time the blood pressure has regained its normal level. Hence the failure to observe any depression of the blood pressure in survival animals after complete adrenalectomy. Therefore the adrenal glands should not be considered as essential to the maintenance of blood pressure as some earlier workers concluded, but should be described as a normally functioning accessory-mechanism the removal of which causes a transient fall of pressure. It may be noted here that we have frequently observed a marked slowing of the heart rate after adrenalectomy. The normal rate slowly returns during the recovery process. That the recovery process is not wholly due to the acceleration in heart rate is indicated by the fact that the recovery process is not completed after excision of a portion of intestine (*vide supra*).

Further, we believe that these facts adequately explain the low blood pressure in Addison's disease. Due to disease of the adrenal glands, there is lack of adrenaline and the consequent fall of blood pressure cannot be compensated because of the fibro-caseous involvement of the abdominal ganglia. Hence a persistently low blood pressure.

#### SUMMARY

Experiments have been performed upon anaesthetised and decerebrate cats demonstrating a fall of blood pressure when adrenaline is prevented from reaching the general circulation from the adrenal glands.

In order to obtain such a result it is essential that the collateral circulation should be tied as well as the adrenal veins.

The fall is not permanent, and the slow recovery is probably dependent upon vaso-motor control of the splanchnic area.

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# ESTROGENIC SUBSTANCES: I. APPARATUS AND METHODS FOR PREPARATION OF STABLE EXTRACTS FROM NATURAL SOURCES

JAMES C. JANNEY, M.D., F.A.C.S., AND BURNHAM S. WALKER, Ph.D.  
From the Evans Memorial and Boston University School of Medicine  
BOSTON, MASS.

The introduction by Allen and Doisy (1) of the vaginal spread method of testing for the ovarian hormone has led to an enormous number of investigations involving the induction of estrus in castrated female animals. The literature on this subject has been assembled and correlated in the valuable monograph of Frank (2), who gives a bibliography of 491 titles covering the literature up to 1929.

Since the publication of Frank's monograph, the crystallization of the ovarian hormone has been reported by Doisy, Veler and Thayer (3) and by Bntenandt (4). These discoveries, if substantiated, will constitute the second major advance in the study of the chemical mechanism of estrus, and more broadly, of the chemistry of reproduction in the female.

Substances capable of inducing estrus in castrated female animals apparently have a very wide distribution in nature. Estrogenic material has been obtained from follicular fluid (5), corpora lutea (6), placenta (7), blood (8), urine (9), amniotic fluid (10), liver (11), bile (12), milk (10), testis (13), feces (14), bird's eggs (13), and many plant materials, including yeast (15), grains (13), garden vegetables (16) and flowers (17). Whether or not active materials from different sources are chemically identical is still unknown.

This paper deals with methods for the convenient preparation of actively estrogenic extracts from some of the natural sources. No special claim for originality in principle can be made for any of these procedures. Our purpose is to present *in detail* methods which have been found to combine adequate yield with convenience of manipulation. The majority of published work has emphasized the chemical properties and physiological effects of the extracts, giving only scanty description of the initial stages of preparation.

## EXTRACTION FROM URINE

Urine from women in the last three months of pregnancy was obtained from a maternity home. Collections were made in 15 liter carboys, about 200 cc. of chloroform being added to each carboy before the collections were made, to serve as a preservative, and to add to the chloroform used later as an extraction medium.

We selected chloroform as the solvent from the first, on account of its availability, non-inflammability and freedom from such harmful oxidizing substances as may be present in ether (18).

In the extraction, we avoided the usual procedure of previous concentration. The evaporation of large volumes of urine in open dishes is at best an unpleasant process; vacuum evaporation would involve apparatus beyond our means or those of the average laboratory, unless carried out at a very slow rate. Preliminary experiments with separatory funnel extractions led us to believe that the partition coefficient of the active material between chloroform and water was sufficiently high to permit direct extraction without previous concentration.

The extraction apparatus, which is of the impluviation type, is shown in Fig. 1.\*

An all-glass apparatus is imperative. Rubber stoppers are entirely out of the question, since they are rapidly dissolved by chloroform. Cork stoppers are longer-lived but yield in the extract noticeable quantities of a crystalline material, M.P. 236° C., free from ash, nitrogen, phosphorus or sulfur. This material can be easily obtained by refluxing cork with chloroform and recrystallizing the residue from the evaporation of the chloroform with ethyl acetate.

Extraction is carried out as follows: the urine container, an ordinary 5-gallon glass carboy, is charged with 15 liters of urine and one liter of chloroform. The flask of the extraction apparatus is filled with chloroform (before the carboy is put in place) by dipping the long tube in chloroform and applying suction at the condenser outlet, with the stopcock closed. When the flask is nearly full, the stopcock is opened and the tube removed from the chloroform. The opening of the stopcock prevents siphoning out of the chloroform. After the tube has been inserted into the carboy, the siphon can be started by applying suction at the stopcock. An asbestos board should be placed between the carboy and the electric plate, as shown in the diagram. From then on all that is necessary is to supply current to the electric plate and water to the condenser, to keep the extractor running as long as may be desired. The only possibility of anything going wrong is the occasional leakage of air around the stopcock, resulting in the breaking of the fluid column in the siphon. This has happened a few times, but we have not greased the stopcock lest we contaminate the extract.

Our time of extraction has been uniformly 16 hours (two working days). We do not recommend leaving the extractors entirely unattended over night, on account of the possibility of failure of the siphon by the (very occasional) leakage of the stopcock.

To remove most of the chloroform extract it is only necessary to remove the extractor from the urine carboy and allow the extract to siphon out. We usually let the small residual chloroform in the bottom of the flask remain and proceed with the next extraction. If it is desired to remove all the extract, it can be poured out through the condenser. The

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\*We are indebted to Mr. F. S. Macalaster, who built the apparatus for us, for certain modifications increasing the compactness and mechanical strength of the extractor, and to Mr. Albert Copans, for making the drawings.

apparatus may be cleaned by filling the flask in the usual manner with 10 per cent alkali, heating to boiling, and then flushing out thoroughly with a stream of water led in through the long tube.

The excess chloroform can be distilled off the extract in any ordinary distillation apparatus, using a steam bath as the source of heat. If stoppers are used they should be protected with tinfoil. A compact all-glass distillation apparatus with a vertical spiral condenser is to be recommended.

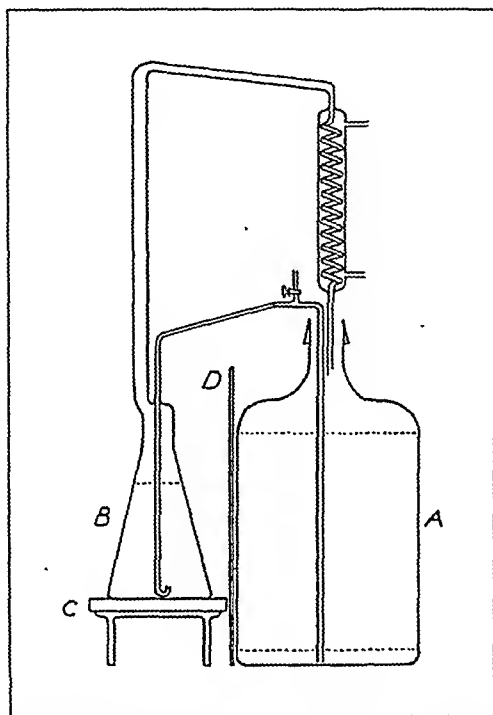


Fig. 1. Extraction apparatus for urine. A, Urine container (5-gallon glass carboy). B, Chloroform flask. C, Electric plate. D, Asbestos board.

The product should be kept in chloroform solution in dark glass bottles with glass stoppers. Under such conditions, as we will show later, extracts do not lose potency in a year at room temperature.

#### EXTRACTS FROM TISSUES

It seemed desirable, if possible, to apply a similar process of continuous extraction to tissues. Most investigators have either desiccated the tissues or used solvents miscible with water. In our experience, drying of tissues either in air or in vacuum (using apparatus available in the laboratory) was uniformly accompanied by a certain amount of decomposition, resulting in loss of potency and introduction of toxic or otherwise objectionable materials into the extract. The use of a water-miscible solvent, such as alcohol, resulted in the extraction of a much larger amount of inert material, most of which was difficult to separate.



Extraction by imbluviation is not applicable to solid material since the solvent will tend to follow definite paths through the material, and portions will remain untouched. With desiccated tissue, simple standing or heating with the solvent is quite satisfactory. Our purpose, then, was to combine the desiccating and extracting processes, allowing the gradual removal of water while the material was in contact with the solvent.

With this in view, an all-glass apparatus was devised, involving the automatic separator of Hultman, Davis and Clarke (19). This apparatus is shown in Fig. 2. The fresh, wet tissue is heated in the flask with chloroform. Chloroform and water distill off together in a definite proportion which depends upon their relative vapor pressures at the temperature of

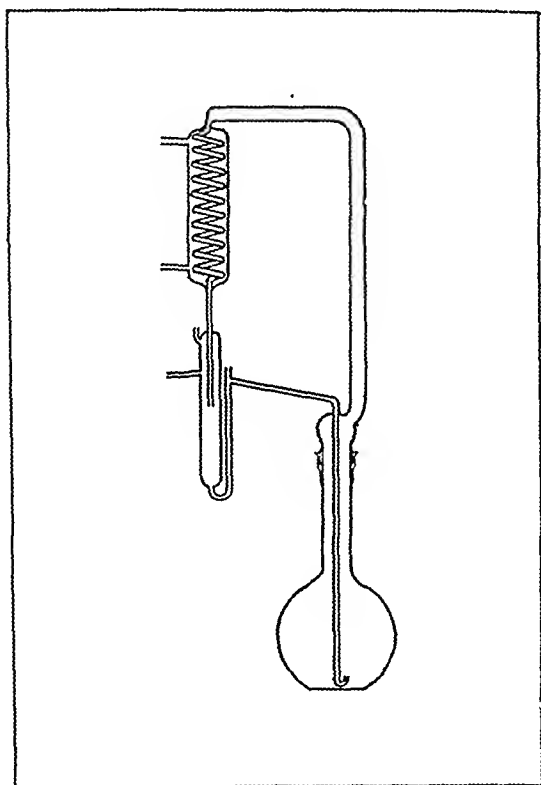


Fig. 2. Extraction apparatus for tissue.

distillation. The vapors condense and pass into the automatic separator where the heavier chloroform sinks to the bottom and is returned to the flask. The water rises and escapes from the side tube.

This process, although rather slow, requires no attention whatever beyond the supply of heat to the flask and water to the condenser. At the medium heat of the electric plate used, about 400 grams of water can be removed from a sample of tissue in eight hours. By the time the water is removed, there is uniform distribution of chloroform-soluble material and the majority of it may be removed by a simple filtration. If complete extraction is desired, a brief repetition of the refluxing with fresh chloroform will accomplish this purpose.

## POTENCY AND STABILITY OF CHLOROFORM EXTRACTS

The crude extract can be tested for its estrogenic power by simply evaporating the chloroform completely (small traces are toxic) from a small aliquot, taking up the residue in 2 cc. oil sesame and injecting the oil solution into a castrated female mouse in three portions, three hours apart. The technique of castration, preliminary control smears, injection, reading of test smears and interpretation is that used by Janney (20). It should be noted that such procedures vary a great deal with different workers and that in comparing results from different laboratories, variations in technique and interpretation must be considered.

We find that amounts of crude extract equivalent to one cc. of original urine are usually sufficient to cause estrus. This figure does not represent the actual concentration of estrogenic material in the urine, since with further purification and the use of an aqueous medium for injection, amounts equivalent to less than one cc. of original urine will produce estrus.

That chloroform extracts suffer no great loss of potency over long periods of time is shown by the following experiment. A portion of a chloroform extract of urine was diluted so that one cc. was equivalent to one cc. of the original urine. This extract was placed in a brown bottle with glass stopper and kept in a closet in the laboratory. One year later, one cc. portions were evaporated, dissolved in oil of sesame and injected into six test mice, all of which gave full positive reactions. The extract had in the meantime deposited a dark, adherent sediment which proved inactive.

## POTENCY AND STABILITY OF AQUEOUS PREPARATIONS

The injection of oil solutions into mice has certain disadvantages; it sometimes remains in the site of injection for many days, occasionally causing extensive sores. We have in all cases preferred injection in an aqueous medium whenever it was feasible. Isotonic sodium chloride solution is the ideal medium for injection. We have observed with surprise that none of the numerous investigators have mentioned this very obvious expedient. Many speak of water suspensions; in our experience water injections always cause sloughing at the site of injection, as well as obvious signs of discomfort on the part of the mouse during injection. Saline suspensions cause the mouse no apparent pain and no bad after-effects.

By using the method of Zondek (21) with the single modification of using saline instead of water as the final vehicle, it is possible to obtain from the crude chloroform extract a preparation with a greater potency per unit of original urine than the crude extract itself. This may indicate either an inhibiting effect of impurities, or more complete absorption from the aqueous medium. A preparation made according to Zondek (saponification of residue from chloroform extract, extraction from aqueous alkaline suspension with ether, suspension of residue from ether evapora-

tion in saline, dilution and injection) with the use of saline as the injection medium, gave the following results:

TABLE I

Urine equivalent of dose	Number of mice	Number positive	Number negative
10 cc.	2	2	0
5	2	2	0
1	2	2	0
0.5	2	2	0
0.1	2	1	1

The preparations by Zondek's method appear to lack stability. Whether kept in the cold or at room temperature, they show loss in potency after a week. This same extract, one week later, was negative in doses equivalent to 2 cc. urine, and two weeks later, negative in doses equivalent to 5 cc.

A more stable aqueous preparation was made by further treatment of the product of the Zondek procedure. A chloroform extract of 420 liters of urine was evaporated just to dryness. The residue was boiled with concentrated sodium hydroxide, cooled and extracted with ether. The ether extract was evaporated to dryness and the residue boiled with 2 per cent acetic acid (420 cc.) and filtered. The filtrate was found to be active, but most of the material remained undissolved. This insoluble residue was dissolved in 95 per cent alcohol, boiled with bone-black and filtered. From the alcoholic solution crystals separated, which were found to be identical with the unidentified solid alcohol described by Marrian (22). In agreement with Marrian, we found that these crystals had no estrogenic activity. The (alcoholic) mother liquor from this crystallization was evaporated to dryness, taken up in chloroform, filtered and the chloroform evaporated off. The residue was extracted with boiling water, which gave a turbid suspension; this was diluted to 250 cc. A number of mouse tests were carried out on this extract, showing that it contained about one-eightieth of the total estrogenic material of the original urine (assuming one mouse unit per cc.). This extract was stable for over four months, as shown in Table II. No special precautions were taken for its preservation, it being kept in an ordinary glass-stoppered flask in diffuse daylight and at room temperature. All doses were made up to 2 cc. with saline.

TABLE II

EXTRACT PREPARED OCTOBER 2, 1929.

Date	Dose (cc. extract)	Number of mice	Number positive	Number negative
Nov. 6	.25	5	5	0
	.13	4	4	0
	.06	4	4	0
Nov. 13	.10	6	6	0
	.01	6	0	6
Nov. 20	.05	2	2	0
Dec. 4	.05	6	5	1
Mar. 24	.05	5	3	2
Apr. 9	.05	9	7	2

Stable aqueous extracts can also be prepared by other slightly different procedures. For the final extraction with boiling water can be substituted the addition, drop by drop, of an ether solution of the active material to saline heated well above the boiling point of ether. The keeping qualities of such a preparation are shown in Table III.

TABLE III  
EXTRACT PREPARED DECEMBER 10, 1929.

Date	Dose (cc. extract)	Number of mice	Number positive	Number negative
Dec. 10	2	5	5	0
Dec. 18	1	5	5	0
Dec. 18	0.5	5	4	1
Mer. 5	2	2	2	0
Mar. 12	1	2	1	1
Mar. 12	0.5	2	2	0

#### TISSUE EXTRACTS

The tissue extractor has not been used for as long a time as the urine apparatus, but has given very satisfactory results. Our type procedure is as follows: the tissue is ground in a meat chopper and introduced into the flask of the apparatus. A volume of chloroform is added at least as great as that of the tissue. The condenser is then attached and heating continued until water ceases to be given off (this requires from 16 to 32 hours with a placenta). The chloroform and water usually form an emulsion in the flask, which clears as the water is eliminated.

When water is no longer given off, extraction is considered complete and the chloroform is filtered from the residual solid. The extract is evaporated to small volume and an excess of sodium hydroxide solution added. The mixture is allowed to saponify half an hour on the steam bath, is then cooled and extracted with ether in a separatory funnel. If an emulsion forms it can be broken by the addition of solid sodium sulfate.

The ether extract is evaporated, taken up in saline and injected without filtering. The amount of extra material is much greater in the tissue extracts than in the urine preparations and the suspensions are quite turbid.

Extracts have been made from placenta and from liver following this procedure; in both cases the minimum effective mouse dose is the equivalent of 5 grams wet tissue. The finding of estrogenic material in the liver is in agreement with the results of Schröder and Goerbig (23), who found that injection of liver lipoids caused growth of the uterus in immature rabbits, and with Dingemanse and Laqueur (11), who found estrogenic material in liver and bile. The bile as a source of estrogenic material has also been studied by Gsell-Busse (12).

#### SUMMARY

1. Apparatus for the convenient extraction of estrogenic material in large quantity from urine and tissue is described.

2. Preparation of crude chloroform extracts (stable for at least a year) and of more purified aqueous suspensions (stable for at least four months) is outlined.

3. Isotonic salt solution is recommended as the most satisfactory injection medium.

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# A METABOLIC STUDY OF DESICCATED SUPRARENAL MEDICATION IN MAN

R. G. HOSKINS AND F. H. SLEEPER

Worcester State Hospital  
WORCESTER, MASSACHUSETTS

Desiccated suprarenal substance has been in use as a therapeutic agent for many years. It is a standard article of commerce in the pharmaceutical trade. There are in the literature many nebulous claims of benefit following its use, but of reports of clean-cut, controlled investigation in human subjects there is a dearth.

For the past three years we have been engaged in a diagnostic-therapeutic study of the subject of dementia praecox. Among some 130 patients subjected to somewhat elaborate diagnostic study, more than half have shown functional deviations from normality that point toward endocrine deficiency. One common picture presented in this disorder is reduction of body temperature, blood pressure, and basal metabolic rate; secondary anemia; and reduction of bodily vigor. This picture is suggestive of adrenal deficiency. In numerous instances suprarenal substance has been administered alone or in combination with other medicaments. The general conditions under which the work was carried out have been previously reported (1).

Among the series of cases so treated, nine have been selected in which satisfactory test conditions obtained. The suprarenal substance was administered by mouth in dosages varying from 18 to 90 grains daily, and for periods of 54 to 108 days. In eight cases the suprarenal substance was used alone; in one, it was superimposed upon a preceding course of thyroid treatment. The subjects were all males, ranging in age from 23 to 40 years.

Before the medication was begun, determinations were made, among other things, of urine volume; total urinary nitrogen; basal metabolic rate; blood pressure; pulse; temperature; erythrocyte count; leucocyte count; percentage of various types of the white cells; non-protein nitrogen; uric acid and sugar in the blood; galactose tolerance; body weight; and "lung volume" as indicated by spirometer measurements. Standard methods of making the various tests were employed, as previously reported (1). In this series, "Suprarenal Emplats" of Parke-Davis & Co. and a special preparation of adrenal cortex made by Reed & Carnrick were administered.\*

An inspection of the accompanying table shows that the results have been essentially negative throughout. Likewise no significant mental

\*It is a pleasure to record our obligation to these firms, as well as to Armour & Co., for generous supplies of suprarenal material.

## Book Reviews

EL SISTEMA NERVIOSO AUTONOMO EN LA REGULACION DE LA GLUCEMIA. J. Puche Alvarez. Rev. méd. de Barcelona, 8: 344. 1927.

The author reports a series of some 50 experiments on the effects of various influences on the blood sugar level. This level was found to be lowered by vagus stimulation, asphyxia after splanchnic and hepatic nerve block, choline (in man and rabbits but not in dogs) and eserine. Pilocarpine caused an increase in the blood sugar in normal animals but augmented the hypoglycemia of adrenal deficiency. Atropine had no demonstrable effect. It is concluded that the autonomic nervous system has an indubitable regulating influence on carbohydrate metabolism through its influence on the endocrine glands especially concerned therewith.

THE FEMALE SEX HORMONE. Robert T. Frank. 1929. Charles C. Thomas, Springfield, Illinois. Pp. 321.

The author has been personally active as an investigator throughout the significant period of development of our knowledge of the subject. He writes, therefore, with an excellent historical perspective. The first section of the work comprises a detailed treatment of the biology, pharmacology and chemistry of the subject. The embryology and anatomy are clearly presented and then a chapter is devoted to physiological experiments, such as extirpation and transplantation of the ovary. The chapter on the experimental results of injecting extracts is especially good. Without detailing further topics treated, suffice it to say that the student will find every modern phase of the subject succinctly treated. The more crucial experiments have mostly been performed originally or have been repeated by the author and his colleagues, hence he shows a firm touch in his critical estimates of the data. The remainder of the book is devoted to clinical considerations. It, too, is good, but is less fresh, since much of the material is more or less commonplace gynecology.

The work is clearly written throughout and is well printed. The illustrations are abundant and generally clear. A well selected bibliography closes each section of the book.

The book as a whole accomplishes admirably what is, one assumes, its fundamental purpose, of putting the reader in close touch with the significant current knowledge throughout the field. It is timely and adequate.

MANUEL DE LAS ENFERMEDADES DEL TIROIDES. G. Marañón. 1929. Manuel Marin, Barcelona. Pp. 211.

Marañón has added another to the list of several recent excellent books on thyroid disease. He has followed what has come to be the conventional plan in writing such books—giving chapters to “physiology,” “anatomy,” etc., then to each of the varieties of thyroid disorder. The book, although exhibiting the author’s catholicity of knowledge of the world’s literature, is of particular significance in its bringing together the outstanding material written in the Spanish language. The work is well printed and the illustrations plentiful and interesting. They are largely from the author’s own experience.

## Abstract Department

Experimental epithelioma in white mice as influenced by adrenal grafts from rabbits treated with the same tumor (*Modifications évolutives de l'épithélioma expérimental de la Souris blanche par greffes de surrénales provenant de Lapins préparés avec ce même épithélioma*). Arloing, F., A. Jossierand and J. Charachon, *Compt. rend. Soc. de biol.* 100: 1035. 1929.

Rabbits were given subcutaneous injections of crushed tumor, a total of 1.9 grams in three doses in nine days. A week later the adrenals were transplanted into tumor-bearing mice. They had an inhibitory effect on the tumor growth not possessed by adrenals from untreated rabbits. This lasted about a week. The adrenals of the injected rabbits showed no gross or microscopic changes a week after the injections stopped. Two weeks after they were doubled in size, the cortex swollen and the medulla degenerated. At this time their inhibitory influence on tumor growth was unreliable. Later, it seemed actually altered, so that the adrenal grafts favored the growth of the epithelioma.—J. C. D.

Relations between changes in the adrenal cortex and alterations in experimental cancer in white mice (*Relations entre les modifications de la cortico-surrénale et l'évolution du cancer expérimental de la Souris blanche*). Arloing, F., A. Jossierand and J. Charachon, *Compt. rend. Soc. de biol.* 101: 646. 1929.

These authors agree with Sokoloff that there is increased activity and later degeneration of the cortex and that in the first phase there is an action of the gland inimical to the tumor.—J. C. D.

Lecithin and lecithin ferment in arterial blood and that of the adrenal (*Lécithine et lécithinases dans le sang artériel et dans le sang surrénal*). Bianco, J., *Compt. rend. Soc. de biol.* 102: 463. 1929.

Observations on the lecithin content and lecithin splitting power of arterial, venous and adrenal blood are given. The animal used is not named. The adrenal pours lecithin into the blood stream and also supplies to it a lecithin splitting ferment.—J. C. D.

Adrenaline vasodilatation. Dunlap, H. H., *J. Physiol.* 67: 349. 1929.

Ether diminishes both the vasoconstriction and cardiac effect of adrenaline. The fall of blood pressure after small doses is due to vasodilatation in skeletal muscles, and diminution of active visceral vasoconstriction.—C. I. R.

Methods for testing for the presence of adrenal cortex hormone. Flory, E., A. Szent-Gyorgyi and M. E. Flory, *J. Physiol.* 67: 343. 1929.

Study of muscular fatigue in cats deprived of adrenal cortex convinced the authors that the method is not reliable for detection of the presence of the cortex hormone.—C. I. R.

Histophysiology of the adrenal in experimental arterial hypertension (*Histophysiologie de la surrénale pendant l'hypertension artérielle expérimentale*). Goormaghtigh, N. and L. Elaut, *Compt. rend. Soc. de biol.* 101: 501. 1929.

Denervation of the carotid sinus and root of the aorta in rabbits produces hypertension. In such animals, the adrenal medulla shows in the first day a rapid exhaustion of adrenin followed over a period of months by an accumulation in excess of normal. Hypertrophy is not noticeable. The cortex shows a rapid reduction in cholesterol in the first day, and then a steady accumulation together with a true hypertrophy of the cortex and numerous mitotic figures in the glomerulosa. This suggests an increase in blood cholesterol. Clinically such cases of hypertension are seen with enlarged adrenals. These results suggest that the adrenal enlargement results from the hypertension and not vice-versa.—J. C. D.



Arterial blood pressure and blood flow in skeletal muscles as influenced by epinephrine. Gruber, C. A., *Proc. Soc. Exper. Biol. & Med.* 26: 472. 1929.

In unanaesthetized cats small doses of epinephrine invariably caused an increase in the rate of blood flow in skeletal muscles irrespective of the change in blood pressure. Large doses of epinephrine rapidly injected intravenously caused an increase in blood pressure accompanied by a decrease in rate of blood flow in skeletal muscle. Following the rise the blood pressure fell below the normal level and simultaneously with it a marked increase in the rate of blood flow through the muscles was observed.—M. O. L.

Effect of yohimbine on adrenin's influence on blood sugar (*Action de la yohimbine sur les effets de l'adrénaline a l'égard du sucre du sang*).

Reinforcement of the hypoglycemic effects of insulin by yohimbine (*Renforcement des effets de l'insuline sur le sucre du sang au moyen de la yohimbine*). Hanson, S., *Compt. rend. Soc. de biol.* 101: 603. 1929.

Yohimbine paralyzes the sympathetic motor nerve endings. As a result, when injected into rabbits, it abolishes the hyperglycemia produced by adrenin and reinforces markedly the hypoglycemia resulting from insulin.—J. C. D.

Effect of adrenalin and cholic acid on creatinin excretion (*Über den Einfluss des Adrenalins und der Cholsäure auf die Kreatininausscheidung*). Kaziro, K. and A. Taku, *J. Biochem.* 11: 203. 1929.

In male rabbits, the hourly and daily excretion of creatinin is increased by subcutaneous administration of adrenalin, and decreased by subcutaneous administration of sodium cholate.—B. S. Walker.

The function of the interrenals in *Torpedo* (*Die Funktion des Interrenalgewebes bei Torpedo*). Kisch, B., *Endokrinol.* 1: 31. 1928.

The interrenals of the *Torpedo*, which are analogous to the cortex of the adrenal gland of higher animals, apparently contain the so-called adrenal hormone, since removal causes muscular weakness followed by early death due to respiratory failure. There are also pigmentation changes. Similar results are not obtained by operation without the removal of the gland. Addition of interrenal extract relieves the symptoms.—B. C.

Thyroid function and the pressor action of adrenalin (*Schilddrüsenfunktion und Blutdruckwirkung des Adrenalins*). König, W., *Arch. f. exper. Path. u. Pharmacol.* 134: 36, 1928.

The pressor responses to injections of adrenalin in various concentrations in normal and thyroidectomized dogs were studied following the subcutaneous administration of thyroxin. It was found that thyroxin administration did not increase the sensitivity to adrenalin in normal animals. Even a longer treatment with thyroxin had no uniform effect on the responses to adrenalin in normal dogs. In thyroidectomized dogs the effectiveness of adrenalin was definitely diminished. The responses could be restored to the normal level by administration of thyroxin. It was concluded that the failure of the thyroid function lessened the reaction toward the sympathicomimetic pressor substance, adrenalin. From the failure of effect of thyroxin administration in certain experiments and from the certain results of thyroxin administration after thyroidectomy it is probably indicated that the thyroxin effect is concerned with the metabolism and not directly with action on any organs.—L. C. Wyman.

Responses of the kidney and spleen to subcutaneously injected epinephrin. Koppányi and M. S. Dooley, *Proc. Soc. Exper. Biol. & Med.* 26: 443. 1929.

In anesthetized dogs massage of areas injected with epinephrin may produce marked localized vasoconstrictor effects, even when the general blood pressure remains unaffected. Kidney and spleen volume changes are more easily elicited with small amounts of epinephrin than a change in general systolic blood pressure.—M. O. L.

The effect of repeated injections of insulin on the suprarenals of rabbits (*Der Einfluss chronischer Insulinzufuhr auf die Nebennieren beim Kaninchen*). Langecker, H., Arch. f. exper. Path. u. Pharmacol. 134: 155. 1928.

Experiments were carried out on growing male rabbits which received a series of injections of insulin, averaging about 30 in the course of one year. The absolute and relative weights of the suprarenal glands, as well as the "standard variation," were determined in both normal and experimental animals. Biological and colorimetric assays of the adrenalin content were also made. It was concluded that the suprarenals of rabbits continuously treated with insulin were, on the average, heavier than those of normal rabbits. The difference was not great but was large enough in order to assume from a study of the standard variation that suprarenal hypertrophy occurred after insulin administration. The determination of the adrenalin content is of value only if estimated at least seven days after the last injection of insulin, since the gland loses its effective pressor substance which is only gradually made up. Despite the diminution of the biological, and according to some authors the morphological demonstrable adrenalin, the colorimetrically determined adrenalin content is unaltered. It can be assumed that the reducing constituent of the gland, which stands in some genetic relation to adrenalin, is in no way affected, and that the pressor substance is secreted under the influence of insulin administration. The suprarenal hypertrophy in the course of continuous insulin administration is due for the most part to enlargement of the cortex, but since the absolute adrenalin content is still greater than normal it is indicated that the medulla is also involved, though to a much less degree.—L. C. Wyman.

Adrenin content in three cases with adrenal tumor. The relation between the histology of the tumor and the patient's blood pressure (*Dosage de l'adrénaline dans trois cas de tumeurs surrénales. Rapports avec la structure histologique de la tumeur et la tension artérielle du malade*). Langeron, L., M. Paget and P. Lohéac, Compt. rend. Soc. de biol. 100: 873. 1929.

Two epitheliomas of the cortex and a sympathetic cell tumor were studied. The adrenin contents did not agree with the histology in one case and in another there was an increased blood pressure although no increase in adrenin was seen.—J. C. D.

The use of epinephrine as a diagnostic test for angina pectoris. Levine, S. A., A. C. Ernstene and B. M. Jacobson, Arch. Int. Med. 45: 191. 1930.

Epinephrine was administered subcutaneously in doses of 1 cc. to three groups of persons; one group of 11 with angina pectoris, a second of 10 of the same average age but without angina, and a third of 10 normal young adults. In all but one patient with angina pectoris, typical pain resulted from the injection. In none of the control patients did this pain occur. Electrocardiographic studies showed that following the injection of epinephrine the T wave in the angina group increased slightly in amplitude, while in the other two groups it showed a tendency to decrease. The increase in blood pressure and pulse rate was somewhat greater in the anginal group than in the others. It is suggested that the production of anginal pain by the injection of epinephrine may serve as a diagnostic test for angina pectoris. The test would not be applicable when the diagnosis is certain but rather in doubtful cases or when there are other possible explanations for the symptoms, such as gallstones or disease of the stomach or the duodenum. Because epinephrine produces typical pain with great regularity in patients with angina pectoris, therapeutic use of the drug in such patients should be carried out with great caution.—Authors' Summary.

Studies on the hormone of the adrenal cortex (*Recherches sur une hormone cortico-surrénale*). de Mira, F. and J. Fontes, Compt. rend. Soc. de biol. 101: 602. 1929.

An extract of entire adrenal gland made in salt solution and freed from adrenalin was injected into decapsulated rabbits. It was found to relieve muscular fatigue as tested by an ergograph.—J. C. D.

Similarity of action between histamine and adrenin on tired rabbit muscle (L'action de l'histamine sur les muscles fatigués du Lapin est semblable à celle de l'adrénaline).

Action of adrenin on tired muscles from decapsulated rabbits (Action de l'adrénaline sur les muscles fatigués du Lapin décapsulé). de Mira, F. and J. Fontes, *Compt. rend. Soc. de biol.* 102: 209, 211. 1929.

Adrenin in small doses revives the fatigued extensor foot muscles in normal and decapsulated rabbits. Histamine in doses twice as great as those of adrenin produces the same results, which are due to an increased blood supply following capillary dilation. These results suggest that the power of cortical extracts to revive tired muscle, which is thought to indicate a cortical hormone, is actually the result of small traces of adrenin or some histamine-like product formed during the preparation of the extract.—J. C. D.

Action of the toxins of botulinus and of anaphylactic shock on the chemical composition of the adrenal (Action de la toxine botulique et du choc anaphylactique sur la composition chimique des surrénales). Mouriquand, G., A. Leulier and P. Sedallian, *Compt. rend. Soc. de biol.* 100: 682. 1929.

The botulinus toxin reduces the amount of adrenin but not of lipoids when injected into guinea pigs; that of shock has no effect.—J. C. D.

Hyposuprarenalism. Peterman, M. G., *Am. J. Dis. Child.* 37: 1238. 1929.

A case of possible hyposuprarenalism in a boy of 13 years of age is reported. The outstanding features were the history of tuberculosis and possible Addison's disease in the father's family and in the patient, the history of weakness, lassitude, easy fatigability, vaso motor instability, gastro-intestinal irritability, lowered resistance to infection, repeated attacks of acidosis, bronze skin, low blood pressure, sweating of the hands, hypoglycemia, acid intoxication and ketosis. Post mortem examination revealed an almost complete destruction of the suprarenal glands by fatty degeneration.—M. B. G.

Adrenin and acidosis (Adrénaline et acidose). Raffin, R. and P. Saradjichvili, *Compt. rend. Soc. de biol.* 102: 560. 1929.

A study of the results of intravenous and subcutaneous injections of adrenin lead the authors to conclude that it produces retention of chlorine to a point approaching acidosis and an elimination of other acid ions in the urine.  
—J. C. D.

Physiological studies of malignant cells (A preliminary communication). Sokoloff, B., *Am. J. Physiol.* 90: 521. 1929.

A combination of iron and an extract of whole suprarenal gland was found to possess the property of regulating the nucleo-cytoplasmic ratio of certain protozoa. Prolonged action of this material causes liquefaction of the protoplasm. The iron and suprarenal extract with the addition of tri-naphthypararosanilin sulphate was found to have a selective destructive action on the malignant cells of four types of tumors in mice and rats.—M. O. L.

Blood supply to suprarenals (Über die Blutversorgung der Nebennieren). Sotoluchin, A., *Ztschr. f. Anat. u. Entwicklungsg.* 90: 288. 1929.

It is suggested that some of the interrelations of the suprarenals and sex organs may be due to a common blood supply.—A. T. R.

The action of ephedrine on the blood sugar (with a note on its action on the denervated pupil of a cat). Teyko, E. and G. Mekes, *J. Physiol.* 68: 247. 1929.

This substance increases blood sugar in rabbits. The antagonism for insulin is very weak in the rabbit but more pronounced in the dog; there is a synergy between ephedrine and epinephrine in the latter animal. Ephedrine did not affect the denervated pupil of a cat.—C. I. R.

The adrenal and pancreatic diabetes (Surrénale et diabète pancréatique). Turcatti, E., *Compt. rend. Soc. de biol.* 102: 466. 1929.

In dogs, removal of the pancreas and adrenals together or at different times prevents the appearance of hyperglycemia during the short period the animals survive. Denervation of the adrenals does not prevent the appearance of diabetes.—J. C. D.

Adrenin as a factor in the dissociation of gasses in the blood (*Rôle de l'adrénaline comme facteur de dissociation des gaz du sang*). Vacek, T., *Compt. rend. Soc. de biol.* 102: 267. 1929.

If potassium ferricyanide and adrenin are added to blood, there is more gas released than if ferricyanide alone is added. This is due to the adrenin regardless of its reaction. It would seem from these and other experiments that adrenin reacts with ferricyanide to form some gas, probably carbon dioxide.—J. C. D.

The alkaline reserve after adrenalin injections (*La reserve alcaline apres injection d'adrénaline*). Vallagnose, L., E. Herzfeld and J. Gautrelet, *Am. J. Physiol.* 90: 543. 1929.

The alkaline reserve was measured in dogs by Van Slyke's volumetric method after the injection of 1/10 mgm. of adrenaline chloralose. There was almost immediately a marked increase (10-40 per cent) of short duration. Five minutes later the alkaline reserve reached its normal degree; it then lowered progressively. A drop of 40 per cent after two hours was recorded.  
—J. Gagnon.

The reduction of the toxicity of adrenin by the hypotensive substance of the pancreas (*Sur l'atténuation de la toxicité de l'adrénaline par la substance hypotensive du pancréas*). Vaquez, P. Gley and N. Kisthinos, *Compt. rend. Soc. de biol.* 100: 1088. 1929.

The authors have separated a blood pressure reducing extract which, while frequently present with insulin in commercial preparations, is an entirely distinct substance. When rabbits are treated with it, they are undamaged by otherwise lethal doses of adrenin.—J. C. D.

Choline and the adrenal capsule (*Choline et capsules surrenales*). Viale, G. and T. Combes, *Compt. rend. Soc. de biol.* 102: 461. 1929.

Two dogs were decapsulated. Injections of adrenin failed to produce an increase of choline in the blood, as is the case in animals with intact adrenals. This is evidence that the adrenal cortex is the source of such choline. The vagus nerve on one side was cut sub-diaphragmatically in seven dogs, and, after twenty-one to sixty days, the choline content of the adrenal on the cut side estimated. Section of the vagus did not influence the choline content.  
—J. C. D.

Utilizing the splenic contractions produced by adrenin in operations on the spleen (*De L'utilisation de la spléno-contraction adrénalinique pour les opérations spléniques*). Weil, P. E. and R. Gregoire, *Compt. rend. Soc. de biol.* 100: 637. 1929.

In one case out of three, an injection of adrenin reduced the size of an enlarged spleen so that there was very little hemorrhage at operation.—J. C. D.

On the reversal of the effect of adrenaline upon the rabbit's intestine and the toad's limb vessels. Yen, T. J., *Tohoku J. Exper. Med.* 14: 415. 1930.

In an elaborate 36-page table Yen reviews the literature on the reversal of the reaction to adrenaline in various organs with change of dosage or other conditions. He adds the results of a personal study of the phenomenon using rabbit intestine and the perfused leg of the toad. Reversal of reaction was infrequently seen in intestinal preparations supplied with air, but when adre-

naline aerated for 20-30 minutes was applied to the preparations reversal was invariably seen. It is ascribed to decomposition products of oxidized adrenalin. Very few instances of reversal of effect with change of dosage were seen in the toad-leg preparations.—R. G. H.

**Influence of the thyroid, suprarenals and nervous system on production and treatment of peptic ulcer.** Crile, G. W., Society Proceedings of the Southern Surgical Association, Dec. 10-12, 1929. Abst., J. A. M. A. 94: 290.

Clinical and experimental evidence indicates that hyperacidity and hypermotility are controlled by the nervous system and the thyroid and suprarenal glands, which exhibit a reciprocal relation. The thyroid gland controls the permeability of every cell of the organism. The suprarenal glands are an integral part of the nervous system, especially of the sympathetic system, which in turn is the greatest activator of the thyroid gland. It is logical to expect, then, that gastric ulcer could be controlled by excision of sufficient thyroid or suprarenal tissue to reduce the drive of the sympathetic nervous system. A reciprocal, independent group of organs forming a working system apparently is best modified by removing a part of each. Accordingly, partial thyroidectomy and suprarenalectomy were performed in five cases of intractable or recurrent ulcer of the stomach, followed in every case by a decrease in gastric and intestinal motility and disappearance of the symptoms of ulcer.

**The endocrine glands from procreation to death** (*Les glandes endocrines de la procreation a la mort*). Levi L., Rev. franç. d'endocrinol. 7: 294. 1929.

A review is given of some of the literature concerning the relation of the endocrines to human development from conception to death. The various endocrinopathies of the different ages, e. g., foetal life, pre-puberty, middle age and old age are discussed, and endocrine therapies which have proved helpful are described.—B. C.

**Recklinghausen's disease and pluriglandular disturbances.** Mosbacher, F. W., Arch. f. Psychiat. 88: 163. 1929. Abst., J. A. M. A. 93: 1422.

Mosbacher discusses the various aspects from which the etiology of the disease has been reviewed. Older authors have studied the microscopic changes; recently the problem has been brought up in connection with disturbances of internal secretion. The case reported may be considered as representing a typical example of this interrelation, and Mosbacher infers that the conception of neurofibromatosis must be extended to include the simultaneous occurrence of endocrine disturbances and to consider all cases in which this is not evident as exceptions. The history of the patient revealed hereditary insanity. One of his brothers was nervous and one was slightly acromegalic; two others were without taint. Up to his eighteenth year the patient was perfectly normal; marked growth of his hands and feet then occurred and he was subject to attacks of melancholy. Lack of concentration, impatience, fidgeting, excitement and other symptoms of mental disturbance, together with headaches and pain in the region of the kidneys, were present. Histologic examination of a small tumor obtained from the left arm presented the picture of a neurofibroma. The basal metabolism was considerably disturbed, which together with the symptoms of acromegaly was characteristic for hyperfunction of the pituitary body and thyroid. The deficient development of secondary sexual characteristics indicated involvement of the genital glands, and diffuse pigmentation of the skin was symptomatic for participation of the suprarenals. To which of these symptoms the slight mental disorder should be ascribed, was not clear; however, the hereditary factors may be partly responsible.

**Heteroplastic pluriglandular grafts on man as treatment of endocrinopathies** (*Impianti pluriglandolari eteroplastici nell'uomo per la cura dell'Endocrinopatie*). Pende, N., Rass. Clin. Scient. Ist. Biochim. It. 6: 3, 1928.

The author takes a firm stand against the theory of rejuvenation, while he believes it possible to delay by grafts the senescence, not of one but of several endocrine glands. The treatment is indicated for delayed somatic, psychic and sexual development in adolescent subjects with endocrine alterations and also for amenorrhea due to hypoovarism or hypoovarism and hypopituitarism and for adiposity of hypophyseal, ovarian or thyroid origin. The

conclusions of the author on his 14 cases are that the effect is not promptly seen. At times it takes 3 to 4 months before it shows. The technic must be correct and should not give any reaction of fever. The only phenomenon happening almost constantly and without serious consequences is a crisis of polyuria and arterial hypotension on the day following the operation. The operative wound heals remarkably quickly. As to the good effects of this treatment there cannot be any doubt, when following it, a woman who had her menopause 22 years before actually had reappearance of menstruation for over two years. Rather than to attribute the good effect to absorption of autolytic material derived from the grafted glands Pende believes in a reduced vitality of the glands, which allows them a certain degree of hormonal functionality. The effect of such grafts is only temporary (one year or more, according to Pende's observations), but in spite of it their usefulness is beyond doubt. As a final conclusion the problem of the pluriglandular graft is based on the correct endocrine diagnosis of the patient and on the consequent rational therapy. Monkey glands (hypophysis, thyroid or gonads) are used, grafted around the external vaginal coat of the testes and in women in the deep retro-mammary tissue.—G. V.

Constitution and human races (*Konstitution und Rasse beim Menschen*). Saller, K., *Ergebn. d. Anat. u. Entwicklungsg.* 28: 250. 1929.

In connection with a discussion of the factors underlying constitutional types, there is a brief review of some of the speculations that have been advanced regarding the rôle of the various endocrine organs in determining these characteristics.—A. T. R.

The internal factors of development. Hormones and the nervous system (*Les facteurs internes de la croissance. Hormones et système nerveux*). Aron, M., *Rev. franç. d'endocrinol.* 7: 269. 1929.

The current views of the hormone control of development are reviewed. Evidence is presented, based upon grafting experiments, that two regions of the central nervous system are especially involved in development. Early development through germ layer formation may be controlled by the innate power of the fertilized ovum. After the formation of the nervous system the control passes to it, and when the endocrines originate, at least in certain Amphibians, control is partly invested in them.—B. C.

Cryptorchism in horse, pig, dog and cat, histological study (*Untersuchungen über Kryptorchismus beim Pferd, Schwein, Hund und bei der Katze, unter besonderer Berücksichtigung der mikroskopischen Anatomie*). Bötschi, A., *Ztschr. f. Anat. u. Entwicklungsg.* 89: 727. 1929.

Largely of morphological interest. The author does not agree entirely with the idea that adult retained testes are essentially of a juvenile or foetal type.—A. T. R.

A new test for normal and experimental changes occurring during the oestrous cycle in guinea pigs (*Un test nouveau des modifications spontanées et provoquées de l'oestrus chez la Souris*). Bourg, R., *Compt. rend. Soc. de biol.* 102: 592. 1929.

Histologically the lipoid granules in the cells of the uterine epithelium of guinea pigs and rats undergo cyclic changes during oestrous. They disappear during preoestrous and reappear in metoestrous. These same alterations occur when the cycle has been brought on in a spayed animal by the use of folliculine.—J. C. D.

Compensatory hypertrophy of the untreated ovary after unilateral X-ray sterilization. Brambell, F. W. R. and A. S. Parkes, *Proc. Roy. Soc. B.* 105: 36. 1929.

In each of 107 mice, 4 weeks old, the right ovary was sterilized by irradiation. The left ovaries underwent complete compensatory hypertrophy as judged by weight of the ovary and size of the litter. The number of follicles maturing at each oestrus and the number of resulting corpora lutea were approximately equivalent to those of two normal ovaries.—E. L.

**Decidual reactions of the mucous membrane of the uterus and their connection with the internal secretion of the ovary** (*Réactions déciduales de la muqueuse utérine et leurs rapports avec la sécrétion interne de l'ovaire*). Brouha, L., *Liège méd.* 21: 1211. 1928. *Abst., Rev. franç. d'endocrinol.* 7: 324.

In order that the gravid transformation of the uterine mucous membrane may take place there must be the action of two hormones taking place, folliculine and the hormone secreted by the corpus luteum acting in a definitely established time relation.—Translated by J. Gagnon.

**Effects of urine from pregnant women on the male genital tract** (*Action de l'urine de femme gravide sur de tractus génital male*). Brouha, L. and H. Simonnet, *Compt. rend. Soc. de biol.* 101: 368. 1929.

Male mice received daily for ten days injections of urine from a two months pregnant woman. In young mice, genital growth was hastened, particularly that of the accessory sex glands. In adults, these glands hypertrophied. This is a more delicate test for pregnancy than the changes produced in the female mouse. The changes may be due to anterior hypophysis substance in the urine. After three months pregnancy, folliculine becomes prominent in the urine and overshadows the hypophyseal secretion, so that such urine then has an inhibitory influence on the genital tract.—J. C. D.

**Effect of the age of the recipient and of the grafted ovary on the oestrous cycle in the white rat** (*Influence de l'âge de l'animal récepteur et de l'ovaire greffé sur le cycle oestral du Rat blanc*). del Castillo, E. B., *Compt. rend. Soc. de biol.* 102: 457. 1929.

Adult ovaries grafted into adult hosts thrive best and survive up to one and a half years. Immature ovaries grafted into adult hosts grow for a while but are eventually absorbed, while adult ovaries in hosts before puberty do not grow. The hosts were spayed. The transplants were made into the kidney. The effectiveness of the grafts was judged by the vaginal smears. The presence of grafted ovarian tissue was confirmed by autopsy.—J. C. D.

**The basal metabolic rate in relation to the menstrual cycle.** Conklin, C. J. and J. F. McClendon, *Arch. Int. Med.* 45: 125. 1930.

From a study of 10 subjects it was concluded that the basal metabolic rate tends to reach its lowest level following menstruation and its highest level preceding menstruation. A deficient diet decreases not only the basal metabolic rate but also the duration of menstruation and the length of the menstrual cycle.—R. G. H.

**Neutralization of the follicular hormone in a pregnant female which was spayed** (*Neutralisation de l'hormone folliculaire chez la femelle gésante castrée*). Courrier, R., R. Kehl and R. Raynaud, *Compt. rend. Soc. de biol.* 100: 1103. 1929.

Guinea pigs will carry fetuses to normal delivery, if spayed late in pregnancy. Folliculine injected into a spayed, but not pregnant animal, produced vaginal changes in three days. When injected into a pregnant female it had no effect. It produced no vaginal changes in a spayed pregnant female. This result indicates that there may be some mechanism besides the corpus luteum to neutralize folliculine in the pregnant animal.—J. C. D.

**Observations on the standardization of the water-soluble oestrus-producing hormone.** Dickens, A. T. and E. C. Dodds, *J. Physiol.* 68: 348. 1930.

Detailed outlines of precautions necessary are given, including strict asepsis in ovariectomy, diet and standard technic. Injections were made twice daily during these days of 0.2 cc. of the extract. Vaginal smears were made on the first and second days and twice on the third and fourth days, the last three smears being mixed with a drop of water. Evaluation of smears is discussed in detail. Other methods of administration are also discussed.—C. I. R.

The simultaneous production of two hormones by the corpus luteum. Frank, R. T., R. G. Gustavson, Helen McQueen and M. A. Goldberger, *Am. J. Physiol.* 90: 727. 1929.

The same batch of pink corpora lutea of the sow was extracted with alcohol and then extracted by the technic described by Hisaw (dialyzation through collodion membrane). The ether fraction was injected into castrated rats and gave a positive reaction for the presence of the female sex hormone. The aqueous fraction gave a positive test for the presence of the corpus luteum hormone (weakening the symphysis pubis of the virginal guinea pig). It is thus demonstrated that the corpus luteum contains two different hormones, the one corresponding to that of the follicle and the placenta, the other a cycle inhibiting and nidatory hormone.—R. T. Frank.

The significance of the occurrence of oestrin in male urine. Free, A. R., G. F. Marrian and A. S. Parkes, *J. Physiol.* 67: 377. 1929.

A substance was extracted from male urine that is identical in physiological action with oestrin as indicated by vaginal cornification and uterine hypertrophy. The kidney does not actively secrete or concentrate this substance. Oestrin added to the heart-lung-kidney preparation is not excreted or absorbed and does not disappear when incubated with shed blood. Disappearance when injected is due to oxidation.—C. I. R.

Studies in ovulation. I. The relation of the anterior pituitary body to ovulation in the rabbit. Free, A. R. and A. S. Parkes, *J. Physiol.* 67: 383. 1929.

Hypophysectomy within an hour after copulation inhibits ovulation.  
—C. I. R.

Physiology of corpus luteum. IV. Production of artificial deciduomata with extracts of the corpus luteum. Goldstein, L. A. and A. J. Tatelbaum, *Am. J. Physiol.* 91: 14. 1929.

Bilateral ovariectomy and traumatization of the uterine mucosa were performed on virgin guinea pigs on fifth day after oestrus and followed by five daily subcutaneous injections of either corpus luteum extract (as prepared by Corner and Allen), or estrogen, or mazola oil. Autopsies were performed on the sixth day after operation. Deciduomata were formed at point of trauma in those animals treated with corpus luteum extract. The animals treated with estrogen and mazola oil showed no growths. Deciduomata were also produced in normal animals (with ovaries intact and no injections) by similar traumatization. The experiments confirm the observation that corpus luteum extract contains a special hormone which has for one of its functions the sensitization of the uterine mucosa of the guinea pig so that deciduomata are formed upon indifferent stimulation of the endometrium during the proper period of the sexual cycle.—L. A. Goldstein.

Ovarian follicular hormone. Janney, J. C., *Arch. Surg.* 18: 1241. 1929.

The work reported is based on 203 injections of castrated female white mice in an effort to confirm the dependability of the blood test for oestrus-producing hormone as previously reported by Frank and Goldberger. The technic of the experiments was, with one or two exceptions, kept as nearly identical with Frank's technic as was possible. The reason for the changes made has been fully discussed. Frank's method of reading the smears has been followed. The curve obtained from the pregnant patients, from whom blood was obtained for control, approximated the results already reported by Frank. The curve obtained from the bloods secured at various periods of the menstrual cycle did not agree in any of the essential particulars with Frank's results and the blood test is considered too unreliable for clinical use. Although this series is larger than the number reported by Frank neither one, nor the combination, is sufficiently large to form a dependable criterion of the reliability of the test.—Author's Abst.



**Effect of castration on muscle (Influence de la castration sur la musculature).** Jasienski, J., *Compt. rend. Soc. de biol.* 101: 533. 1929.

The author studied cattle, guinea pigs, chickens, rabbits and frogs. The striking changes were best shown by steers and frogs and consisted of a marked reduction in the diameter of the individual muscle cells in the castrates.  
—J. C. D.

**Production of precocious puberty by parabiosis (Puberté précoce par parabiose).** Kallas, H., *Compt. rend. Soc. de biol.* 100: 979. 1929.

Sixteen female albino rats, 15 to 20 grams in weight, were parabiotically united to spayed females of the same age. The vagina opened 7 to 9 days later and the oestrous cycle was established. This early maturity is considered as due to the double quantity of pituitary hormone acting on a single set of ovaries.—J. C. D.

**Precocious development of the genitalia in male rats by parabiosis (Développement précoce de l'appareil génital chez le Rat male infantile en parabiose).** Kallas, H., *Compt. rend. Soc. de biol.* 102: 552. 1929.

Pairs of young rats, one of which was a normal male and the other a gonadectomized animal of the same age, were united by parabiosis. Abnormally rapid sex development of the normal male took place, which was identical with that produced by transplants of the pituitary. This result followed whether the gonadectomized animal was male or female.—J. C. D.

**Rut and the corpus luteum (Rut et corps jaune).** Lipschütz, A. and L. Adamberg, *Compt. rend. Soc. de biol. (Paris)*, 102: 282. 1929.

Guinea pigs were subjected to spaying and then to implantation of ovarian tissue into the kidney. They showed active oestrous followed by prolonged four months dioestrous. The grafts showed corpora lutea and large follicles. These latter were of such size that they could be regarded as active endocrine organs. Evidently then the secretion of the corpora lutea blocked the action of the follicular hormone, possibly by a desensitizing action on the uterus, vagina, etc.—J. C. D.

**Compensatory reactions of the testicle of the guinea pig after unilateral castration (Réactions compensatrices du testicule du cobaye après castration unilatérale).** Lipschütz, A. and E. Viñals, *Compt. rend. Soc. de biol.* 100: 984. 1929.

Testicular weight has been compared in normal and unilaterally castrated animals of the same litter 9 to 13 months after birth, the operation having been performed several days after birth. In the majority of cases testicular weight was greater in the experimental animals. There were 2 cases in which the testicle attained a weight which was 72 and 94 per cent higher than that of one normal testicle in the control animal. But if the weight as attained by the testicle in the experimental animals is compared with the maximal weight in normal animals, then there were only 4 cases in which testicular weight in the experimental animal was greater, whereas in 9 cases testicular weight was not beyond normal maximal weight. The difference between the experimental maximum and the normal maximum was only about 20 per cent. These data are in favor of the theory that compensatory hypertrophy of the testicle after unilateral castration is to be explained by acceleration of growth in such a manner that the maximal testicular weight in unilaterally castrated adult animals is sooner attained than is the case in normal ones. The extra-testicular factor responsible is probably the hypophysis.—A. Lipschütz.

**Compensatory reactions of the ovary of the guinea pig after unilateral castration (Réactions compensatrices de l'ovaire du cobaye après castration unilatérale).** Lipschütz, A., *Compt. rend. Soc. de biol.* 100: 986. 1929.

Former experiments suggested that hypertrophy of ovarian fragments is an integrative phenomenon based on the law of follicular constancy. This makes it probable that ovarian hypertrophy can be explained on the same lines as testicular hypertrophy in mammals. One hundred fifty-nine ovaries

of the guinea pig at different ages have been weighed. The maximal ovarian weight is by no means attained at puberty. The relation between the maximal and the minimal ovarian weight varies according to age or body weight, being 7.7 at a body weight of 100 to 200 grams and 2.7 at a body weight of 600 to 700 grams. Evidently the possibilities of attaining the maximal weight are quantitatively characteristic of each age and these possibilities are greater the older the animal. In unilaterally castrated animals the difference between the experimental and the normal minimal ovarian weight was 81 per cent; on the contrary, the difference between experimental and the normal maximal weight was only 31 per cent. Evidently the possibilities of attaining the maximal ovarian weight characteristic of a certain age are greater when only one ovary is present. All these data can be dynamically understood if the law of follicular constancy is taken into consideration. The maximal ovarian weight after unilateral castration can indeed be greater than the normal maximal ovarian weight; but the difference between the experimental and the normal maximum is not very pronounced and from a dynamic point of view the difference can be explained as caused by the fact that the ovary in the unilaterally castrated animal reaches the potential normal maximum sooner. The same general principles underlie the compensatory reactions in the testicle and in the ovary.—Author's Abst.

Folliculine and diuresis (*Folliculine et diurèse*). Lipschütz, A. and E. A. Wilckens, *Compt. rend. Soc. de biol.* 102: 553. 1929.

Spayed guinea pigs were injected with folliculine alone or with folliculine and quantities of fluid, which would promote diuresis. The oestrous cycle was re-established and persisted for the same length of time, regardless of whether fluid was injected with the folliculine or not. Since an increased output of urine does not reduce the effect of the folliculine on the oestrous cycle, little of the folliculine is eliminated through the kidneys under normal conditions. The elimination of large quantities in the urine during pregnancy must be regarded as a response to special conditions.—J. C. D.

The assay of oestrin. Marrian, G. F. and A. S. Parkes, *J. Physiol.* 67: 389. 1929.

A method for a standardization is described with a discussion of the variable factors.—C. I. R.

The treatment of endocrine disturbances in menstruation. Martin, F., *Deutsche med. Wchnschr.* 54: 989. 1928.

The disturbances in menstruation considered are irregular and profuse flow in individuals in whom there is no pathological change in the uterus or ovaries. The extent of the dysfunction of any particular component of the endocrine system can not be measured. Therefore, it is a matter of chance whether one can treat that portion of the organ complex which is at fault. Rather than attempt to regulate the individual components of the endocrine system, the author advocates stimulation of metabolism by improving the living conditions, which refers to place of abode, climate, habits, state of nutrition as well as psychic factors. Four cases are reported in which no specific medication was used, but unsatisfactory hygienic conditions were corrected with the result that the symptoms are relieved.—M. R. White.

Exchange of hormones in animals in parabiosis. Passage of the ovarian hormone from the normal to the spayed animal (*Échanges hormonaux chez les animaux en parabiose*). Passage de l'hormone ovarienne des sujets normaux aux sujets chatrés).

Oestrous cycle in normal and spayed rats in parabiosis (*Cycles oestraux chez les rats normaux et chatrés vivant en parabiose*). Martins, T., *Compt. rend. Soc. de biol.* 102: 605, 614. 1929.

When a pair of female rats, one spayed and one normal, are united by parabiosis, the normal animal shows a prolonged break in the oestrous cycle. This is followed by the appearance of cyclic changes in the vaginas of both

animals showing that the ovarian hormone passes from the normal to the spayed animal and influences its genital tract. The ovaries of the normal animal are enlarged and present a picture similar to that following administration of anterior lobe substance. The uterus of the spayed rat is undersized but not atrophic to the extent found in untreated spayed animals. The guinea pig shows similar evidence of the passage of ovarian hormone.—J. C. D.

The seminal vesicle of the white mouse as a test for the testicular hormone (Utilisation des vésicules séminales de la Souris blanche comme test des hormones testiculaires). Martins, T. and A. Rocha e Silva.

Action of testicular extracts on the vesicles of castrated mice (Action des extraits testiculaires sur les vésicules séminales des Souris chatrées). Martins, T. and A. Rocha e Silva, *Compt. rend Soc. de biol.* 102: 480, 485. 1929.

Following castration, within five days, there are marked cytological changes in the vesicle. In less than two weeks, there is marked shrinkage of the entire vesicle. Using the product of length times width as an index, this index falls to half its former value. These changes can be prevented by injections of extract from bull and goat testis. The article is illustrated. Directions for making the extract by treatment with alcohol, benzol, and subsequent saponification are given. This work agrees with that of Moore and Gallagher on the white rat, published about the same time.—J. C. D.

Induction of menstruation in women by use of ovarian hormone. McClendon, J. F., G. Burr and F. F. Wildebrush, *Proc. Soc. Exper. Biol. & Med.* 26: 430. 1929.

In a case of amenorrhea of 5 months duration in a woman 19 years old the injections of 1000 mouse units of ovarian hormone daily for 9 days was followed by a menstruation three weeks later. In a second case of 5 years duration in a woman 22 years old a menstruation occurred after two series of injections totalling 15,000 mouse units.—M. O. L.

A case of eunuchoidism (Über einen Fall von Eunuchoidismus). Munro, *Ztschr. f. Konstit.* 14: 401. 1928.

The report concerns a man of 59 described largely from postmortem examination. There was absence of body hair, marked hypoplasia of the testis and moderate hypoplasia of the external genitalia. There was tallness, moderate prognathism, and marked atrophy of the prostate. Numerous anthropological measurements are given which show that this is a typical case of eunuchoid tallness with the disproportions of the condition, such as greater length of the lower part of the body when compared with the upper part, increased span of the arms, delicate bones, long thin extremities, relatively wide pelvis and very small shoulders. On histological examination the testis was seen to consist of a great overgrowth of interstitial cells, with atrophic seminiferous tubules. The thyroid and adrenal were somewhat hypoplastic.  
—W. J. A.

Influence of the sex hormones on the basal metabolism. Experiments with females (Influence des hormones sexuelles sur le métabolisme basal. Essais expérimentaux chez les femelles). Ptassek, L., *Compt. rend. Soc. de biol.* 100: 1250. 1929.

In bitches, as in male dogs, castration results in a decline in the basal metabolism, followed by a temporary return toward normal, and then a fall in metabolic rate. This is then maintained permanently at 50-60% of the original rate.—J. C. II.

Gynecomastia (Zur Kenntnis der Gynäkomastie). Schmidt, O., *Ztschr. f. Konstit.* 14: 588. 1929.

From the literature, the author gathered 179 cases of gynecomastia. A great many of them had genital disorders; 47 of them were examined anatomically and proven to be cases of actual hypertrophy of the mammary gland.

Of the thirteen cases in which the testes had been examined histologically, eight showed testicular atrophy and four contained tumors. This suggests some relation between gynecomastia and abnormal testes, although there is also much to be said for the chromosomal origin. Many cases had other endocrine disorders that might influence the testes and thus indirectly be related to the hypertrophy of the male mammary gland. Twenty-four additional cases were found in the Russian literature too late to be included in the analysis.  
—A. T. R.

Significance of the blood supply, internal pressure and interstitial cells in the biology of the testis (Über die Bedeutung der Vascularisation, des Binnendruckes und der Zwischenzellen für die Biologie des Hodens). Schweizer, R., *Ztschr. f. Anat. u. Entwicklungsg.* 89: 775. 1929.

A discussion of the rôle of the blood supply, structure and position of the testis in spermatogenesis. The interstitial cells are considered factors in regulating the blood supply by exerting direct pressure on the small vessels and by modifying the general internal pressure in the testis as a result of their atrophy and hypertrophy.—A. T. R.

Clinical observations on the use of an ovarian hormone; Amniotin. Sevringhaus, E. L. and J. S. Evans, *Am. J. Med. Sc.* 178: 638. 1929.

The effect of amniotin, an ovarian hormone secured from the amniotic liquor of cattle, has been studied on 25 women with menopausal and menstrual disturbances. Its use has been of marked value in the relief of the vasomotor phenomena of the menopause, and in promoting feminine development of one woman of infantile type.—Authors' Summary.

Comparative morphology of the interstitial tissue of mammalian testis (Zur vergleichenden Morphologie des Zwischengewebes im Säugerhoden). Silbermann, U., *Ztschr. f. Anat. u. Entwicklungsg.* 90: 597. 1929.

A description is given of the histology of the interstitial tissue of about 14 species.—A. T. R.

Sex glands and adaptive ability. Tsai, L. S., *Science*, 71: 106. 1930.

The experiments deal with the effect of castration upon problem box and maze performances by white rats. At the age of about five months, twelve rats had both of their testicles removed (total castration), eight had only one testicle removed (semi-castration), and seven were put through a control operation. After one week of preliminary training, they were required to solve a single-platform box problem once a day for four weeks. Then they were given a week of preliminary training in the maze which they were required to learn once a day during the next two weeks. The maze experiment was repeated on eight totally castrated and eight control animals for four weeks. The results indicate that the totally castrated rats are inferior to the semi-castrated and the control animals in their adaptive ability as measured by the speed in solving the problem box as well as by both speed and accuracy in maze performance.—Author's Abst.

On the pregnancy-response of the uterus of the cat. Van Dyke, H. B. and R. G. Gustavson, *J. Pharmacol. & Exper. Therap.* 37: 379. 1929.

If the hypogastric nerves of the cat are stimulated, it is well known that the non-pregnant uterus relaxes, while the pregnant uterus contracts. The attempt has been made to cause this pregnancy-response in ovariectomized and non-ovariectomized virgin or non-pregnant cats by the subcutaneous administration of various extracts. The following results were obtained: Ovariectomy did not alter the response of the non-pregnant cat's uterus. Ovariectomy in the pregnant cat, accompanied in our experiments by fetal resorption was without effect unless fetal resorption was complete. In the latter case the uterus behaved like a non-pregnant uterus. A foreign body introduced into the non-pregnant uterus had no effect on the response. Placental and follicular-liquid extracts provoked marked uterine hypertrophy without any

pregnancy-reversal of the uterus. Extracts of early vascularized and late vascularized corpora lutea, ovarian residue, uterus and fetus caused little or no uterine hypertrophy and no alteration of response. Lipoidal extracts of mature corpora lutea caused pronounced uterine hypertrophy in experiments with three kittens. A contraction of the uterus simulating pregnancy repeatedly occurred in two of these experiments when the hypogastric nerves were stimulated. Aqueous extracts of mature corpora lutea administered with placental hormone also caused this reversal simulating pregnancy in two of three animals. This effect seemed specific for corpus-luteum extract and probably was due to a substance other than that provoking estrus.

—Authors' Summary.

The dosage and action of pituitary extract and of the ergot alkaloids on the uterus in labor, with a note on the action of adrenaline. Bourne, A. and J. H. Burn, *J. Obstet. Gynec. Brit. Emp.* 34: 249. 1927. *Abst., Physiol. Absts.* 14: 402.

Observations were made on patients in labor. A small rubber bag was inserted with aseptic precautions into the uterus between the membranes and the wall, past the head of the foetus. A record of the pressure changes inside the bag was obtained by way of a manometer on a moving drum. It was found that in a series of 12 primiparous patients a dose of 2 units of pituitary extract, injected during the first stage of labor, never produced untoward effects. Provided the os was at least half dilated, the increase in uterine contractions was usually great enough to shorten the course of labor materially. Tyramine, even in a dose of 10 mgm. given intravenously, produced only a trace of effect on the uterus. Histamine given subcutaneously in doses of 1 mgm. (base) temporarily quickened the rate of contraction, but the effect of even 2 mgm. did not last more than 45 minutes, and the response to this dose was great enough in force to lead to subsequent exhaustion. Ergotamine in doses up to 1-10 mgm. produced a prolonged increase in the tone of the uterus, so that there was no full relaxation between each contraction. The effect of ergot preparations must therefore depend on the amount of specific alkaloid present, and not on histamine and tyramine. Evidence is given showing that ordinary clinical methods do not suffice to distinguish between active and inactive extracts. It is shown that ether inhibits the contractions of labor, though not the contraction produced by ergotamine. It is also shown that adrenaline (0.3 cc.) intravenously inhibits the contraction of the uterus in labor.

Oxytocin and vasopressin. A further examination of the separated principles of pituitary (Posterior Lobe) extract. Burn, J. H., *Quart. J. Pharmacol.* 1: 509. 1928.

The two principles, Oxytocin and Vasopressin, separated from posterior lobe, were examined as to distribution of the antidiuretic and insulin-inhibiting properties. The antidiuretic effect was studied on a human by a method described by the author in the same issue (p. 496), consisting of finding the time required to reach a maximum rate of urine excretion after drinking a liter of water simultaneously with subcutaneous injection of the extract to be tested. Pituitrin was used as a standard of comparison. A chart is given showing that not more than a trace of antidiuretic activity is present in Oxytocin, while Vasopressin has this activity to the same extent per unit of pressor activity as has Pituitrin. The inhibiting effect upon the hypoglycemic action of insulin was determined by injecting insulin plus the extract to be tested into a starved rabbit. Hourly blood sugar values were compared with those obtained one week later in the same rabbit when given insulin alone. A table and chart are given to show that Oxytocin has no power to prevent the hypoglycemic action of insulin, while Vasopressin has a considerable effect. Only one rabbit was used for each test.—I. W. Grote.

Effect of insulin on the precocious puberty produced by hypophyseal transplants (*Action de l'insuline sur l'apparition de la puberté précoce provoquée par implantation d'hypophyse*). del Castillo, E. B. and C. Calatoni, *Compt. rend. Soc. de biol.* 102: 455. 1929.

Daily doses of one insulin unit did not retard the rapid appearance of puberty following pituitary transplants in four white rats.—J. C. D.

The action of posterior pituitary pressor extract on the rabbit's vascular system. Clark, G. H., *J. Physiol.* 68: 166. 1929.

Rabbits fed on dried thyroid for 14 days or more invariably died shortly after intravenous injection of pituitary extract in amounts that gave no obvious symptoms in normal rabbits. Oxytocin was not effective, the results being due to Pitressin. Death was due to cardiac depression. This was not due to vagal activity; the author suggests that the extract affects the coronary vessels. The reason for thyroid sensitization was not determined.—C. I. R.

A crystalline substance of the hypophysis which promotes follicular growth. Claus, P. E., *Proc. Soc. Exper. Biol. & Med.* 27: 29. 1929.

A crystalline product insoluble in absolute alcohol was prepared from the anterior lobe of the hypophysis, which induced precocious sexual maturity when injected in aqueous solution into 18-day-old mice. Another fraction from the anterior lobe soluble in absolute alcohol did not induce precocious sexual maturity but did promote lutein tissue formation and disintegration of ova in the ovaries.—M. O. L.

On the way extracts of the anterior lobe of the hypophysis act (*Sur le mode d'action des extraits hypophysaires antérieurs*). Courrier, R. and R. Kehl, *Compt. rend. Soc. de biol.* 100: 711. 1929.

Alkaline extracts of bovine glands in small doses produce in cats follicular development in the ovary with characteristic accompanying changes in the genital tract. Heavy doses result in a corpus luteum like degeneration of the ripe follicles.—J. C. D.

Possible water balance; effects of alkaline anterior pituitary extracts. Downs, W. G. and E. M. K. Gelling, *Proc. Soc. Exper. Biol. & Med.* 27: 63. 1929.

Mice receiving alkaline extracts of the anterior lobe gain weight more rapidly than do the controls, but their tissues contain from 6% to 8% more water and about 3% less ash than the tissue of controls.—M. O. L.

Pituitary extract and the CO<sub>2</sub> combining power of the blood plasma. Draper, W. B. and R. M. Hill, *Proc. Soc. Exper. Biol. & Med.* 27: 33. 1929.

In normal dogs the intravenous injection of commercial pituitary extract is followed immediately by a marked fall in the CO<sub>2</sub> combining power of the blood plasma. Both the oxytocic and pressor principles of the posterior lobe produced this acidosis.—M. O. L.

On the oxytocic properties of blood from a woman in labor (*Sur les propriétés oxytociques du sang de la Femme en travail d'accouchement*). Fontes, J., *Compt. rend. Soc. de biol.* 102: 227. 1929.

The uterus of a guinea pig was divided and each horn exposed to identical conditions except that one was bathed in defibrinated blood from a woman in labor and the other in blood from a man. The blood from the woman produced active and sustained contractions, that of the man had little effect. Blood taken from a woman eight days after delivery lacked oxytocic properties.—J. C. D.

Studies in Water Diuresis. II. The excretion of urine after hypophysectomy and decerebration. Free, A. R., *J. Physiol.* 68: 305. 1929.

Total hypophysectomy followed by decerebration did not increase urine output or chloride excretion. Alimentary diuresis occurs normally in the decerebrate, hypophysectomized animal and is inhibited by pituitrin. If the operation was followed by renal denervation, large amounts of hypotonic urine were produced. Pituitrin reduced this and increased the chloride percentage.—C. I. R.

**Diabetes insipidus and lesions of the mid-brain.** Report of a case due to a metastatic tumor of the hypothalamus. Fitcher, T. B., *Am. J. Med. Sc.* 178: 837. 1929.

A case of diabetes insipidus due to an alveolar carcinoma of the hypothalamus, secondary to a primary carcinoma of the lung, and without an involvement of the pituitary, is reported. The case would naturally tend to support the view held by many that diabetes insipidus is due to a disturbance of certain regulatory centers in the hypothalamus. The studies supporting the pituitary and hypothalamic conception of the origin of the disease are reviewed. Reference is made to the fact that it now seems amply demonstrated that there are definite nerve fibers connecting the tuber cinereum and the posterior lobe of the hypophysis. The belief is expressed that, although there may be certain centers in the hypothalamus regulating water exchange in the body, the evidence seems very strong that disturbance of the action of a diuretic-antidiuretic hormone produced in the posterior lobe of the pituitary is a very important factor in the etiology of the disease, possibly by sensitizing these centers or by influencing their functions.—Author's Summary.

**The effect of the hormone of the hypophysis on water and salt economy in persons with normal kidneys and diseased kidneys** (*Über die Wirkung des Hypophysenhinterlappens auf Wasser und Kochsalzhaushalt von Nierengesunden und Nierenkranken*). Gutmann, H., *Arch. f. Verdauungskr.* 42: 551. 1928.

Patients with normal kidney function and normal blood pressure were chosen for the experiment. They were given 1 liter of tea, but no food at seven o'clock in the morning. Urine was passed at half-hour intervals and the amount, specific gravity and sodium chloride content were recorded and plotted on a chart. In a later experiment the same procedure was followed except that fifteen minutes before the ingestion of the 1 liter of fluid an intramuscular injection of 2.0 cc. Pituglandol was given. In the control experiment the total urinary output and the specific gravity indicated increased excretion in the first hour. When Pituglandol was injected there was water retention reaching the maximum 1½ hours after the injection. The initial diuresis observed in animals given Pituglandol was not seen in these human subjects. While the water retention lasted the sodium chloride percentage was increased and the specific gravity was correspondingly increased. The duration of the water retention phase was from 2½ to 5 hours. Following the water retention phase there was a phase of compensatory diuresis during which a large volume of dilute urine was passed. After several hours the total urine and total salt excretion were the same whether the patient had been given Pituglandol or had not been injected. Five cases of kidney sclerosis with moderately high blood pressure were tested. In the first of these, after the 2 cc. injection of Pituglandol had been given, the total urine excreted in 12 hours was 800 cc., whereas in a previous test without Pituglandol the urinary output was 950 cc. After an injection of Pituglandol there was a phase of water retention similar to that observed in normal patients after the same treatment. The phase of compensatory diuresis was slower in coming on in these cases with kidney disease than in normal patients. It was evident that although the Pituglandol effect lasted longer, it was not as pronounced in these patients with kidney disease as in normal patients. Later experiments on patients with more badly diseased kidneys demonstrated the fact that the greater the kidney disturbance the less was the action of Pituglandol. The author does not consider it proved, however, that the pituitary hormone acts directly upon the kidney.

—E. P. Bugbee.

**The anti-diuretic effect of the separated principles of the pituitary body.** Hemingway, A. and J. M. Peterson, *J. Physiol.* 68: 238. 1929.

The effects of pitocin and pitressin on water diuresis in man and on heart-lung-kidney preparations were investigated. By the latter method both caused decreased urine volume and increased concentration of chlorides. Pitressin is a vasoconstrictor to the renal vessels. After the ingestion of a liter of water in man, diuresis was inhibited.—C. I. R.

**Simmond's disease (La maladie de Simmonds).** Herman, C., *Rev. franç. d'endocrinol.* 6: 301. 1928.

A woman with a condition diagnosed as Simmond's disease presented an unusual physiognomy with a general appearance similar to that of a mummy.

The eye-brows were completely absent and the teeth had been lost, and there was thinning of the hair of the head and pubes. She showed a diminution in intelligence which was thought to be due to the nutritional changes. Treatment with thyroid extract had been without benefit. The author then treated the patient with an extract of the anterior lobe of the hypophysis by daily injections, and noticed improvement in the psychic condition, although the disease continued. The patient's appetite was greatly improved and intense hunger was felt two to three hours after each injection. There was increased growth of the nails and of the hair in the axillary and pubic regions. The author believes that such a condition is caused by disease of the anterior hypophysis and that it is frequent in women at about the time of the menopause.—R. C. Moehlig.

The exchange of hypophyseal substance in parabiosis (*Sur le passage de substances hypophysaires pendant la parabiose*). Kallas, H., *Compt. rend. Soc. de biol.* 102: 280. 1929.

Young female rats were united in pairs and one of each pair was spayed. Study of these showed that the precocious puberty induced in the unspayed animals of these pairs was marked by a transitory stage of active oestrous, followed by a prolonged dioestrous. The appearance of this latter condition could be accelerated by injections of hypophyseal extract into the spayed animal. This is further evidence of the passage of hypophyseal substance from one animal to another in parabiosis.—J. C. D.

Further researches on the anterior lobe pituitary hormone (*Weitere Untersuchungen über das Hypophysenvorderlappenhormon: Prolan*). Laquer, F., *Am. J. Physiol.* 90: 424. 1929.

The anterior lobe of the pituitary can cause an early maturity of the sex organs, particularly the ovaries, in young female rats. Upon this fact Zondek and Aschheim base their test for the anterior lobe pituitary hormone. They have also found that this hormone is excreted in the urine during pregnancy. Researches concerning this have shown that young rats are in many respects better for the demonstration of the hormone than are young mice. Some of the chemical properties of the hormone are already known, particularly its great sensitivity to acids and alkalies, as well as its instability at a high temperature, have been confirmed. They also sought to find if the hormone on account of its action on the female genitals influenced the growth of the young animal. No action could be determined. Also Prolan can not change the blood sugar of rabbits. It is assumed, therefore, that the hormone known as Prolan excreted in the urine during pregnancy is an active endocrine function of the anterior lobe pituitary acting on the sex organs but having no effect on growth and metabolism.—J. Gagnon.

Basal gaseous metabolism of giant rats. Lee, M. O., H. M. Teel and J. Gagnon, *Proc. Soc. Exper. Biol. & Med.* 27: 23. 1929.

Basal gaseous metabolism determinations were made in four giant rats which had received for four months extracts of fresh beef anterior lobe containing the growth-promoting principle. The basal metabolic rate in these animals averaged 12% less than that of their normal controls. Three weeks after the cessation of administration of the extracts, the basal metabolic rate had risen to approximately the level of the controls.—M. O. L.

Action of various pituitary extracts on the effects of insulin (*Action des diverses substances hypophysaires sur l'effet de l'insuline*). Magenta, M. A.

Action of extracts from the posterior lobe of the hypophysis on the sensitivity of hypophysectomized dogs to insulin (*Action des substances rétro-pituitaires sur la sensibilité à l'insuline des Chiens privés d'hypophyse*). Houssay, B. A. and M. A. Magenta, *Compt. rend. Soc. de biol.* 102: 428-429. 1929.

In dogs a sufficient dose of oxytocin reduces the hypoglycemic action of insulin, while vasopressin has no such effect. Hypophysectomized dogs go into convulsions after smaller doses of insulin than do normals. Oxytocin is very much more effective in relieving such animals than vasopressin.—J. C. D.



Hypophyseal dwarfishness (Hypophysärer Zwergwuchs). Lucke, H., Ztschr. f. Konstit. 14: 430. 1929.

A description is given of a 12½-year-old girl with the development of about a 6-year-old child. During the next 2½ years she was treated with "Präphyson" tablets. Each tablet contains .3 g. dry pars anterior of hypophysis and corresponds to 1.8 g. fresh gland tissue. Three tablets were given per os for 1½ years and then 2 tablets per day the last year. During these 2½ years she grew 28 cm. in height and reached the proportions of a normal 12-year-old girl.—A. T. R.

The effect of anterior pituitary preparations administered during dietary anoestrus. Marrian, G. F. and A. S. Parkes, Proc. Roy. Soc., S. B. 105: 248. 1929.

Anoestrus in rats was induced by a vitamin B deficient diet. The anoestrus period commences at the beginning of loss of body weight. Refeeding with a complete diet caused a return of oestrus. The administration of whole pituitary glands from rats caused the onset of oestrus in 2-3 days. This stimulation of the degenerating ovary is due to the stimulation of the large number of small follicles which are not affected by dietary deficiency. The ovary stimulating substance is present in normal amounts in the anterior pituitary glands of males on a diet deficient in vitamin B.—E. L.

Effects of transplanting anterior lobe of the hypophysis from frogs into young mice (Sur les effets de l'implantation du lobe antérieur de l'hypophyse de Grenouilles chez les Souris infantiles). Martins, T., Compt. rend. Soc. de biol. 101: 957. 1929.

Such transplants have no effect on the growth rate of the genital tract in mice.—J. C. D.

The "all or none" law for the testicle and the hormones of the anterior lobe of the hypophysis (La loi du "Tout ou Rien" du testicule et les hormones du lobe antérieur de l'hypophyse). Martins, T., Compt. rend. Soc. de biol. 102: 483. 1929.

Injectons and implantations of anterior lobe or its hormone over a period up to ninety days failed to produce hypertrophy in the testes or genital tracts of white mice.—J. C. D.

The effects of the ocytotic and hypertensive principles (hormones) from the posterior lobe of the pituitary gland on basal metabolism (L'effet des principes (hormones) ocytotique et hypertenseur du lobe postérieur du corps pituitaire sur le métabolisme basal). Nitzescu, I. I. and J. Gavrila, Compt. rend Soc. de biol. 102: 184. 1929.

By testing these substances on eight normal persons, it was shown that the hypertensive substance produced the rise in basal metabolism, which is usually seen after injections of posterior lobe extract.—J. C. D.

Hereditary microcephaly. Acromicria and the adipose-genital syndrome (Microcephalie familiale. Acromicrie ed syndrome adipeux-genital). Parhon, C. T. L. Ballif and N. Lawrence, Rev. franç. d'endocrinol. 7: 308. 1929.

The authors report the cases of a microcephalic brother and sister, whose paternal aunt was also microcephalic. The condition is thought to be hereditary. Microcephaly is a symptom of acromicria as opposed to acromegaly. The boy showed marked adiposity and double cryptorchidism.—B. C.

Anterior lobe, the thyroid stimulator, V. Basal metabolism. Schwartzbach, S. S. and E. Uhlenhuth, Proc. Soc. Exper. Biol. & Med. 26: 389. 1929.

The effect of several preparations of the anterior and posterior lobe of the hypophysis on the metabolism of ambystoma larvae was studied by Winkler tests. Larvae of two species were used, unanesthetized and in chloretone

anesthesia. Feeding of either anterior or posterior lobe preparations was without effect on the metabolism. Intraperitoneal injections of an extract of beef anterior lobe caused a 30 to 50% increase in the average oxygen consumption of unanesthetized larvae and a 114% increase in anesthetized larvae.

—M. O. L.

The oxytocic substance of cerebrospinal fluid. Van Dyke, H. B., P. Bailey and P. C. Bucy, *J. Pharmacol. & Exper. Therap.* 36: 595. 1929.

The oxytocic substance of cerebrospinal fluid appears to be calcium. Reduction of the calcium to a concentration equalling that of an artificial "cerebrospinal fluid" bathing the isolated uterus abolishes the oxytocic action and yet causes no destruction or removal of true posterior-lobe oxytocic principle. Properly preserved human ventricular and lumbar fluids of normal calcium concentration have an oxytocic effect. The melanophore-expanding effect of cerebrospinal fluid and serum may be due to differences between their calcium concentrations and those of artificial fluids used in the limb-perfusion method of assay.—Authors' Summary.

Liver and thyroid: Hyperfunction of the liver in Basedow's disease (*Leber und Schilddrüse: Die Hyperfunktion der Leber bei Basedowkranken*). Pende, N., *Endokrinol.* 1: 161. 1928.

On the basis that certain functional tests give opposite results in Basedow's disease and cases of known hepatic deficiency, Pende concludes that the liver produces a hormone that is synergistic with that of the thyroid. Hyperthyroidism results in an excess of this liver hormone. This conclusion is supported by the observation of excessive bile secretion in hyperthyroidism. Various theoretical corollaries of this conception are outlined.—R. G. H.

Can the islets of Langerhans transform themselves into acinar tissue? (*Les îlots de Langerhans font-ils retour aux acini?*). Bierry, H. and M. Kollman, *Compt. rend Soc. de biol.* 101: 17. 1929.

Frogs, marmots, and pigeons were examined during periods favorable to such a change, when the acinar tissue was increasing rapidly, as after hibernation. There was no indication of islet tissue altering to form acinar cells.

—J. C. D.

Dextrose insuline equilibrium (*L'équilibre dextrose-insuline*). Bouckaert, J. P., P. Denayer and R. Kerkels, *Compt. rend. Soc. de biol.* 101: 511. 1929.

Two tables are given showing the amounts of glucose necessary to balance a given dose of insulin in normal rabbits.—J. C. D.

Glucose-insulin equilibrium (*Équilibre glucose-insuline*). Bouckaert, J. P., P. De Nayer and R. C. Kerkels, *Arch. internat. de physiol.* 31: 180. 1929.

Glucose solution, rendered isotonic with sodium chloride, was injected from a burette-like apparatus into one of the ear veins of an immobilized rabbit. The other ear was used for injecting insulin and drawing blood. By varying the amounts of insulin and glucose injected, the authors determined the following relationships: The maximum amount of glucose per hour which can be caused to disappear by insulin injection into a rabbit is 1.26 gram per kgm. of body weight. The maximum quantity of insulin which can be utilized by the rabbit for glucose destruction per kgm. of body weight is 6.8 units. Amounts of insulin above this are inactive.—E. L.

The physiological significance of the primary insulin hyperglycemia (*Die physiologische Bedeutung der primären Insulinhyperglykämie*). Bürger, M., *Am. J. Physiol.* 90: 302. 1929.

Intravenous injection of insulin has as a consequence a temporary increase of the blood sugar in man and in animals. The degree of blood sugar increase is dependent upon the vascular region in which the insulin injection takes place, upon the size of the insulin dose, and upon the glycogen content of the liver. In man an average increase of 20 per cent in blood sugar appears 5 to

10 minutes after the intravenous injection of  $\frac{1}{2}$  unit of insulin per kgm. body weight. With corpulent people and myxedematous patients the blood sugar may rise 50 per cent over the initial value under similar conditions. After direct injection of 1-2 units of insulin into the portal vein or one of its branches the increase of blood sugar averaged 35.3 per cent in 21 tests on dogs. If the insulin is injected in the jugular vein and the circulation of blood in the liver is stopped by ligation of the liver hilus the increase of blood sugar in the peripheral blood does not take place. The initial hyperglycemia after insulin injection is thus probably due to the discharge of glycogen from the liver. This thesis is proven by glycogen determinations made at consecutive 10-minute intervals upon the dog's liver by means of a special method. The liver after insulin injection in the portal vein regularly becomes poorer in glycogen. This loss of glycogen becomes the greater, the higher the blood sugar value rises after insulin injection. For example, the loss can amount to as much as 50 per cent of the initial value by injecting 2 units of insulin per kgm. of body weight into a 17.5 kgm. dog. The absolute glycogen loss becomes greater, the higher the initial value of the liver glycogen.—J. Gagnon.

**Influence of insulin on the oestrous cycle in the white rat** (*Action de l'insuline sur le cycle oestral du Rat blanc*). del Castillo, E. B. and C. Calatroni, *Compt. rend. Soc. de biol.* **102**: 454. 1929.

In eight animals, daily injections of insulin over varying periods had no demonstrable influence on the cycle.—J. C. D.

**The insulin fattening cure in pulmonary tuberculosis** (*La cure insulinique d'engraissement dans la tuberculose pulmonaire*). Combemale, F., C. Gernez and A. Breton, *Ann. de med.* **26**: 480. 1929.

The optimum dosage of insulin was 30 units per day administered in two injections. The administration of 45-60 units was deleterious. The 32 cases which were treated by this method of fattening always showed an amelioration of the symptoms coincident with the increase in weight. The authors feel that the results of this method are truly remarkable.—E. L.

**Further observations on latent tolerance in diabetics.** Gibson, R. B., *Proc. Soc. Exper. Biol. & Med.* **26**: 449. 1929.

Three diabetic patients under insulin treatment were given high sugar diets. The insulin dosage was gradually reduced and finally stopped. One patient was continued 40 days on the high carbohydrate diet without insulin. In the other two cases insulin had to be resorted to again after about two weeks, but there was an increased hypoglycemic response to small doses.  
—M. O. L.

**Death of a totally depancreatized dog treated with insulin for 57 months.** (*Mort d'un Chien totalement dépancréaté traité par l'insuline pendant 57 mois*). Hédon, E., *Compt. rend. Soc. de biol.* **100**: 698. 1929.

This dog of about 7 kgm. weight received daily two subcutaneous injections of insulin and a general diet, meat, bread, milk and sugar up to 500 calories. He remained in good health under these conditions, but there was no evidence of better utilization of carbohydrates. For several months before death, larger doses of insulin were necessary. The dog died in convulsions

probably due to hypoglycemia. Marked emaciation, fatty degeneration of the epithelial cells of the kidney tubules, and a thickening of the adventitia of the blood vessels generally, were the only pathological changes found.—J. C. D.

**Insulin and CO<sub>2</sub> combining power of blood plasma in normal dogs.** Hill, R. M. and W. B. Draper, *Proc. Soc. Exper. Biol. & Med.* **27**: 31. 1929.

In four normal dogs after the subcutaneous administration of insulin there was within 40-50 minutes a slight rise in the CO<sub>2</sub> combining power of the blood plasma, followed by a pronounced fall to a level considerably lower than the initial. The authors consider that the results indicated that insulin may intensify a non-ketogenic acidosis. The dosage of insulin used in the experiments was 2 or more units per kilogram.—M. O. L.

Effect of insulin with simultaneous administration of cyanide (*Beiträge zur Wirkung des Insulins bei gleichzeitiger Anwendung von Blausäure*). Hosoda, N., *J. Biochem.* 10: 383. 1929.

Sublethal injections of cyanide induce hyperglycemia in rabbits, which can be controlled by insulin. This is evidence that insulin is not the activator of hexose-diphosphate formation.—B. S. Walker.

Results of continuous insulin injections in depancreatized dogs (*Effet des injections continues d'insuline chez le Chien dépancraté*). Houssay, B. A., J. T. Lewis, V. G. Foglia, *Compt. rend. Soc. de biol.* 101: 241. 1929.

A continuous injection of about one one-hundredth unit of insulin per kgm. per hour serves to keep the blood sugar of a depancreatized dog normal. —J. C. D.

Pancreas and blood sugar regulation (*Papel de páncreas en la regulacion de la glucemia 2aCom*). Houssay, B. A., J. T. Lewis and V. G. Foglia. *Rev. Soc. Argent. Biol.* 5: 1. 1929. *Abst., Physiol. Absts.* 14: 446.

Insulin was injected intravenously into dogs, (a) normal, (b) pancreatectomised, (c) pancreatectomised with a pancreas grafted in the carotid artery and jugular vein. The drop in blood sugar was similar in the 3 series of experiments. The recovery was slightly more rapid in series (b) than in series (a). In series (c) the recovery was much slower. This is taken as proof of the existence of inhibitory fibres in the extrinsic innervation of the pancreas. In their absence, the pancreatic graft continues secreting insulin in spite of the low blood sugar level, and so hypoglycemia is prolonged, whilst in the normal dogs the recovery is prompter because the insulin secretion is inhibited when the blood sugar falls.

Endocrine function of normal and denervated pancreas during insulin hypoglycemia (*La fonction endocrine du pancréas normal ou énérvé pendant l'hypoglycémie insulínique*). Houssay, B. A., J. T. Lewis and V. G. Foglia. *Compt. rend. Soc. de biol.* 101: 239. 1929.

Dogs with pancreatic grafts to replace the extirpated pancreas recovered from the hypoglycemia more slowly than controls. This slow return of blood sugar to normal is due to a retarded response of the graft, which continues secreting an excess of insulin for a longer period than if it had its proper nerve supply.—J. C. D.

The initial hyperglycemic influence of insulin (*Action hyperglycémianté initiale de l'insuline*).

On the mechanism producing the early hyperglycemia following insulin (*Sur le mecanisme de l'hyperglycémie initiale provoquée par l'insuline*). Ionesco, D., I. Cosmulesco and M. Tomesco, *Compt. rend. Soc. de biol.* 102: 167, 170. 1929.

This short initial phase was found in dogs, rabbits, and man following intravenous administration. This increase in blood sugar is at a maximum 5 to 13 minutes after injection and varies from 8 per cent seen in a man to 137 per cent seen in a dog. This peak is followed at once by a steady and rapid decline. This rise is dependent on glycogen in the liver, since diabetics with glycogen poor livers do not give it. Paralyzing the sympathetics of the liver in dogs, either by cutting or drugs, does not eliminate the increase in blood sugar, so the action of the insulin must be a direct hormonal one on the liver cells.—J. C. D.

Physiological studies on insulin. *Memoir I.—Rapid disappearance of insulin injected into the blood stream* (*Études physiologiques sur l'insuline. I er-memoire.—Rapide disparition de l'insuline injectée dans le torrent circulatoire*). Képinov, L. and S. Petit-Dutaillis, *Arch. internat. de physiol.* 31: 310. 1929.

The dogs used were anesthetized with chloralose. The carotid artery and jugular vein of the donor and recipient were anastomosed. Insulin (10-30 units) was injected intravenously. Transfusions of blood (180 cc.-1160 cc.)

from donor to recipient were made immediately, 3, 8 and 25 minutes after the injection of insulin. The blood sugar of the donor was always reduced whereas the recipient receiving a transfusion 25 minutes after the insulin injection, maintained a constant blood sugar. The same was true when the transfusion was made after 8 minutes. When the transfusion of small amounts of blood (less than 500 cc.) was made after three minutes there was only a slight diminution in the blood sugar of the recipient. When the amounts of the transfusions were large (about 1000 cc.) there was a lowering of the blood sugar of the recipient. When the transfusion was made immediately after the injection of insulin, the blood sugar of the recipient was markedly lowered. After partial removal of the liver from the circulation of the donor, the transfused blood of the donor which had received insulin 20 minutes previously would still cause a lowering of the blood sugar of the recipient. The authors believe that the liver plays an important part in the fixation of insulin by the tissues.—E. L.

**Pathogenesis of diabetes mellitus of pancreatic origin.** Mauriac, P. and E. Aubertain, *Paris méd.* 1: 440. 1929. *Abst., J. A. M. A.* 93: 242. 1929.

Mauriac and Aubertin discuss the complexity of the pathogenesis of diabetes mellitus and, leaving aside the rôle of disturbance of various endocrine glands (such as the thyroid, suprarenals and hypophysis), the nervous system and the liver, try to explain the mechanism involved in the pathogenesis of diabetes mellitus of pancreatic origin. Placing insulin in contact with the whole blood, blood serum, plasma or erythrocytes of healthy and sick persons, respectively, they observed an inactivating effect of these substances on the insulin. The same results were observed in experiments with extracts of various organs, such as muscles, kidneys or lungs. The inactivation of insulin was greater by the blood of patients with diabetes mellitus and was maximal in the presence of hemolyzed erythrocytes. This was explained by the presence in the erythrocytes of some substance having the power to neutralize insulin. If the permeability of the membrane of the erythrocytes is abnormally increased, this neutralizing substance may inactivate the insulin secreted by a normal pancreas and thus cause hyperglycemia, or the combination of decreased pancreatic secretion and of neutralization of insulin may be present. Only rarely are the pathologic changes in the pancreas so advanced as to explain diabetes mellitus by a deficiency of the pancreatic secretion only.

**Notes on a dog kept alive by insulin for fifteen months following removal of pancreas** *sur un chien dépancraté maintenu en vie pendant 15 mois par l'insuline*). Mauriac, P. and E. Aubertin, *Compt. rend. Soc. de biol.* 101: 52. 1929.

The animal was maintained by replacing the external secretion of the pancreas by feeding pancreatin, and replacing the internal secretion by insulin.

—J. C. D.

**The lipid splitting action of lungs in life as related to the internal secretion of the pancreas** (*La lipodiérèse pulmonaire in vivo et la sécrétion interne du pancréas*).

**The lipid splitting action of the lungs in vitro and the internal secretion of the pancreas** (*La lipodiérèse pulmonaire in vitro et la sécrétion interne du pancréas*). Nitzescu, I. and G. Benetato, *Compt. rend. Soc. de biol.* 101: 71. 1929.

In normal dogs there is a decrease of about 9 per cent in the fats and cholesterol during the passage of the blood through the lungs. This decrease falls to about one-tenth its normal value after removal of the pancreas. A nearly normal decrease takes place, however, if the animals are treated with insulin. The same relations hold in breaking down of fats by pieces of lung in vitro. Lungs from depancreatized dogs show a diminution of this power which cannot be restored by mixing insulin with the excised lung, but which reaches nearly normal figures if the dogs have been treated with insulin previous to the excision of the lung tissue.—J. C. D.

The reaction of the saliva and its resistance to change of reaction in experimental diabetes—effect of insulin (*Réaction actuelle et potentielle de la salive dans le diabète expérimental.—Action de l'insuline*). Peluffo, A., *Compt. rend Soc. de biol.* 102: 468. 1929.

In sixteen diabetic dogs, the pH of the saliva was not much altered, nor was the pH affected by insulin. The alkali reserve was not altered regularly in diabetes, but was increased by insulin.—J. C. D.

Studies on the cardiovascular effects of insulin. Rähkä, C. E., *Skandin. Arch f. Physiol.* 57: 243. 1929. *Abst., Chem. Absts.* 23: 4507.

Intravenous injection of insulin causes a diminution of the minute volume of the heart. This diminution continues for some time and in certain cases is followed by a transient increase. A second injection does not affect the minute volume as much as the first, and may even be without any action. The reduction in the minute volume is due to a diminution of the beat volume of the heart. The blood pressure in the aorta falls for about 10-30 minutes after an intravenous insulin injection, this fall being sometimes preceded by a brief rise in pressure. The fall in pressure is caused by the diminished minute volume and only very rarely also to vasodilation. Generally the fall in the aortic pressure is accompanied by a constriction of the vessels which may become so pronounced that it is responsible for the observed secondary rise in pressure, and this vasoconstriction is attributed to the outpouring of adrenaline under the influence of insulin. Immediately following an insulin injection, the pressure in the pulmonary artery increases, owing to a vasoconstriction. The occasional lowering of the pulmonary arterial pressure seems to be due to the adrenaline effect. Following an insulin injection, the effect of vagus stimulation on the heart is more or less reduced, but this diminution does not generally occur if adrenaline is injected before the vagus is stimulated. These cardiovascular effects of the insulin are shown to be due to changes in the K and Ca content of the circulating medium produced by the insulin.

The absorption of glucose by the blood cells from diabetic dogs (*L'absorption de glucose par les hématies provenant de Chiens diabétiques*).

Does there exist in diabetic plasma a substance which interferes with the absorption of glucose by the blood cells? (*Existe-t-il dans le plasma diabétique une substance modifiant l'absorption globulaire du glucose?*) Rathery, F., R. Kourilsky and Mlle. S. Gibert, *Compt. rend. Soc. de biol.* 100: 643. 1929.

The action of the red cells toward glucose was the same whether they came from diabetic or control animals. There was no evidence that an interfering substance existed in the blood of the diabetic animals.—J. C. D.

Influence of insulin on the absorption of glucose by normal blood cells (*Influence de l'insuline sur l'absorption du glucose par les hématies normales*). Rathery, F., R. Kourilsky and Mlle. Yv. Laurent, *Compt. rend. Soc. de biol.* 100: 726. 1929.

Centrifugal blood cells of normal dogs were treated with insulin in vitro and tested. Insulin did not influence the absorption of glucose.—J. C. D.

Influence of insulin on the absorption of glucose by red cells in diabetic dogs (*Influence de l'insuline sur l'absorption globulaire du glucose chez les Chiens diabétiques*). Rathery, F., R. Kourilsky and Mlle. S. Gibert, *Compt. rend. Soc. de biol.* 100: 728. 1929.

Red cells tested after addition of insulin in vitro and after injection of insulin into the depancreatized dog showed no change in their absorptive power.—J. C. D.

Pruritis. Sparks, R. A., *Missouri State Med. Assoc.* 26: 24. 1929.

In a number of cases of pruritis (anal, scrotal, vulval and general), whether accompanied or not with glycosuria, the administration of insulin was of marked benefit. Some of the cases were longstanding and the patients were able to obtain temporary relief only from cocaine ointment. In one case with the scrotum and penis enormously swollen and raw from scratching,

insulin relieved the itching in three days, the swelling in less than a week. In cases without glycosuria the insulin dosage was at first 2 to 10 units twice daily, then increased to 10 to 20 units twice a day.—Author's Abst.

Contribution to the study of the physiological variations of the internal secretion of the pancreas. Relation between the external and internal secretions of the pancreas (*Contributions a l'étude des variations physiologiques de la sécrétion interne du pancréas. Relations entre les sécretions externe et interne du pancréas*). Zunz, E. and J. La Barre, Arch. internat. de physiol. 31: 20. 1929.

The injection of secretin causes a gradual diminution of blood sugar. This decrease in blood sugar is proportional to the secretagogue action of the secretin. This increased insulin after secretin injection is not dependent on the vagus as it can be produced after section of the vagi. That this is not a direct action of the secretin on the blood sugar, but is an action on the Islands of Langerhans, was proven by transfusion experiments using the author's pancreateo-jugular anastomosis technique.—E. L.

Contributions to the study of the physiological variations of the internal secretion of the pancreas. VII. The hypoinsulinism following the state of hypoglycemia (*Contributions a l'étude des variations physiologiques de la sécrétion interne du pancréas. VII. De l'hypoinsulinémie consecutive aux états d'hypoglycémie*). Zunz, E. and J. La Barre, Arch. internat. de physiol. 31: 162. 1929.

These authors have produced hypoglycemia by several methods, i. e., insulin, hepatectomy and synthalin. The hypoglycemia produces a decrease in insulin secretion. The diminution in insulin secretion is caused by the superior nerve centers acting by means of the vagus. The exact location of these centers is not known—E. L.

Studies on the pH and alkaline reserve in thyro-parathyroidectomized dogs (*Recherches sur le pH et la réserve alcaline chez les Chiens thyro-parathyroidectomisés*). Parhon, C. I., H. Derevici and M. Derevici, Compt. rend. Soc. de biol. 101: 613. 1929.

The authors found no change in the pH, but a diminution in the alkaline reserve.—J. C. D.

Parathyroid tumor and skeletal abnormalities. Snapper, I., Nederl. Tijdschr. v. Geneesk. 73: 4758. 1929. Abst., J. A. M. A. 93: 1851.

Snapper reports that in a man, aged 56, who was affected with marked decalcification of the bones, associated with severe pains, particularly in the legs and knees, it was found that the disease had begun as generalized osteitis fibrosa cystica. There was a pseudo-osteomalacic end-stage resembling that of Recklinghausen's disease. The calcium content of the blood serum was much increased, which was interpreted as an expression of an overactive parathyroid. There was a small tumor in the thyroid. A tumor in one of the parathyroids was suspected and was found at operation. After extirpation of this small tumor, a decided improvement in the patient's condition was noted.

The presence of histamine and acetyl-choline in the spleen of the ox and the horse. Dale, H. H. and H. W. Dudley, J. Physiol. 68: 97. 1929.

A method is described by means of which a substance identified as histamine was isolated from the spleen, also a substance identified as acetylcholine, demonstrating the natural occurrence of the latter in animal tissues. This substance reproduces the effects of true parasympathetic stimulation. It has not been found in the spleen of the dog, cat, monkey or rabbit.—C. I. R.

Experiments on the Bartonella infection in the white rat (*Experimentelle Untersuchungen über Bartonella-Infektion der Weissen Ratten*). Friedberg, S., Endokrinol. 3: 84. 1929.

Rats from Switzerland, Hamburg, Vienna and Berlin show 100% cases of Bartonella and anemia after spleenectomy with death in about 30% of the cases. Two Italian rats did not show any infection after spleenectomy. One

of these was caused to have the disease by blood transfusion from an infected animal. The author believes therefore that he is dealing with an infectious disease. Bartonella infection, unaccompanied by anemia, can be produced by blocking the reticulo-endothelial system in a normal rat with ferric lactate or India ink. This block, if produced after splenectomy, results in a typical Bartonella-anemic symptoms. He concludes that the spleen, through an unknown factor, plays a defensive rôle.—B. C.

Origin of Hassall's corpuscles (*Über die Entstehung der Hassallschen Körperchen*). Juba, A. and P. V. Mihalik, *Ztschr. f. Anat. u. Entwicklungsg.* 90: 278. 1929.

As a result of a histological study of two human foetuses and one newborn and numerous pig foetuses, the authors conclude that Hassall's corpuscles arise by enlargement of reticular cells followed by degeneration of the centrally located cells. Eight good illustrations.—A. T. R.

Studies on the action of thyroxin on heat regulation (*Studien über die Wirkung des Thyroxins auf den tierischen Organismus und insbesondere auf die Wärmeregulation des Gleichwärmblüters*). Abderhalden, E. and E. Wertheimer, *Arch. f. d. ges. Physiol.* 219: 588. 1928.

Rats and mice are much more resistant to thyroxin than dogs, rabbits and guinea pigs. Rats given thyroxin are more sensitive to increased environmental temperature than normals and show a quicker exhaustion of the glycogen store of the liver. There is a lowering of the blood sugar and an increased  $\text{CO}_2$  production.—M. O. L.

Studies on the effects of thyroid glands from normal and treated rabbits on the growth of epithelioma in white mice (*Recherches sur l'action du corps thyroïde du Lapin normal ou préparé sur l'évolution de l'épithélioma expérimental de la Souris blanche*). Arloing, F., A. Jossierand and J. Charachon, *Compt. rend. Soc. de biol.* 100: 665. 1929.

Bits of thyroid, both from normal rabbits and from ones which had received previous injections of a suspension of the tumor, were transplanted into mice. Neither type of graft had any effect on the growth of the tumor in the mice.—J. C. D.

The interrelation of the thyroid and the other organs (*Die Beziehungen der Schilddrüse zu Funktionsgebieten anderer Organe*). Asher, L., *Schweiz. med. Wchnschr.* S. 802. 1927.

The interrelation between the system thyroid-spleen-bone marrow was shown by two series of experiments. Normal rabbits regenerate blood rapidly if Loewys Hämatopoetines are injected. After extirpation of the thyroid the animals did not react towards the same dose of hämatopoetines, but the reaction returned after extirpation of the spleen. Injection of nucleic acid causes hyperleucocytosis in normal rabbits and a characteristic histological picture of the bone marrow. Both reactions of nucleic acid injection disappear after extirpation of the thyroid gland. Again both reactions reappear after the spleen too has been extirpated. Extirpation of the spleen increases the water metabolism of guinea-pigs; thereupon extirpation of the thyroid lowers the level of water metabolism. These facts show antagonistic regulation of water metabolism by thyroid and spleen. The increase of basal metabolism by adrenalin is markedly diminished after extirpation of the thyroid in rats. —Author's Abst.

Effects of thyro-parathyroidectomy on the excitability of the great splanchnic nerve in the dog (*Influence de l'ablation des thyroïdes et des parathyroïdes sur l'excitabilité du nerf grand splanchnique chez le Chien*). Chauchard, A., B. Chauchard and E. Czarnecki, *Compt. rend. Soc. de biol.* 100: 1114. 1929.

This operation affects the response of the organs innervated but not the conducting powers of the nerve.—J. C. D.

The thyroid problem (*Das Thyreoidcaproblem*). Boothby, W. M., *Endokrinol.* 3: 1. 1929.

A general article setting forth particularly the work of the Mayo Clinic and notable for an excellent and extensive bibliography.—R. G. H.



**Experimental hyperthyroidism and sympathetic irritability.** Chamberlain, Beulah, *Proc. Soc. Exper. Biol. & Med.* 26: 459. 1929.

Dogs fed disiccated thyroid substance showed no greater increase in the blood pressure response to adrenin than did normal dogs.—M. O. L.

**The importance of carbohydrate metabolism in hyperthyroidism.**—Charvát, J., *Otolaryngologia Slavica*, 1: 2. 1929.

From several years of clinical investigation the author concludes that there exists no direct antagonism between the thyroid and the pancreas. One cannot say that in hyperthyroidism the endocrine function of the pancreas is checked by the increased activity of the thyroid. The liver of hyperthyroid individuals is labile, owing to the increased sympathetic tonus. It is not able to fix well the administered sugar, and instantly hands it over to the blood. The liver is, therefore, poor in glycogen, and after a sugar test meal the blood-sugar rises above the physiological level. The kidney-sugar threshold rises in a compensatory manner, so that loss of sugar is prevented thereby, and glycosuria appears in only one-fifth of the cases. Sugar is a well-utilizable and necessary matter for hyperthyroid organisms, because it covers very quickly the energetic needs of the tissues, due to an increased basal metabolism. Oxidation of the sugar is higher in hyperthyroidism than in normal conditions, while the storage of glycogen is weaker, its synthesis being inadequate. The autonomous fixation of the sugar by the tissues (without direct influence of insulin) is very active. As soon as the immediate energetic need in the tissues is satisfied, the sugar remaining uselessly in the tissues can flow over into the venous blood and urine, without having been polymerised into glycogen. If glycosuria appears, it is generally of small extent and shows no tendency to develop into true diabetes. If a disproportion of insulin production and carbohydrate plethora takes place, it signifies a relative and functional disturbance only, which can be repaired by the systematic education of the pancreas to a greater internal function. Administration of small doses of insulin is also able to ameliorate this stage. The functional efficacy of the liver in hyperthyroidism is lowered, owing to the lack of glycogen stores. It is necessary to pay attention to this fact in all operative interventions.—R. G. H.

**Cancer of the thyroid gland.** Clute, H. M. and L. W. Smith, *Arch. Surg.* 18: 1. 1929.

The incidence of cancer of the thyroid in 3,389 operative cases in the Lahey clinic was 1.68 per cent. There were 6.4 times as many women as men who had malignant disease of the thyroid. The greatest incidence of the disease was between the ages of 50 and 65. Cases occurred in persons aged 20 and 82. An adenomatous goiter preceded the malignant disease in 94.4 per cent of the cases studied. Histologically, cancer of the thyroid may be divided in to four chief groups: (1) Malignant adenoma; (2) squamous cell carcinoma; (3) giant cell carcinoma, and (4) small cell carcinoma. Cases in each of these groups have a marked similarity in their clinical history and course. Knowledge of the histological group of a cancer of the thyroid gives valuable information as to (a) the chances of recovery of the patient, or (b) the probable duration of life, and (c) the advisability of roentgen treatments. When cancer of the thyroid can be diagnosed clinically, the chances of cure are small. Lowering the mortality of thyroid malignant disease must at present depend on the removal of the premalignant adenoma. Surgical removal and post-operative roentgen treatment give some good results in the first histologic group (malignant adenoma). Treatment has not been of any real value in the other types of malignant disease of the thyroid.—Authors' Abst.

**The passage of the maternal thyroid hormone through the placenta to the fetus** (*Sur le passage de l'hormone thyroïdienne de la mère au fœtus à travers le placenta*). Courrier, R. and M. Aron, *Compt. rend. Soc. de biol.* 100: 839. 1929.

Pregnant dogs were fed an excess of beef thyroid. Their thyroids showed the histological signs of atrophy. The glands of the pups were normal. If the thyroid feeding to the mothers was continued so that there was an excess of

thyroid hormone in the milk, the glands in the pups atrophied. The placenta then prevented the fetus from receiving an excess of thyroid from the mother, i. e., it is not permeable to the thyroid hormone.—J. C. D.

**Tissue respiration and endocrine functions, III. Influence of thyroidectomy on tissue respiration.** Dye, J. A. and G. H. Maughan, *Proc. Soc. Exper. Biol. & Med.* 26: 439. 1929.

Dogs were thyroidectomized when 5 weeks of age. Seven months later the oxygen consumption of finely minced skeletal muscle of the "cretin" pups was 25 to 60 per cent less than that of muscle from normal litter mates of the same sex. The authors adhere to the view that the thyroid hormone exerts an influence upon the oxidative system of body cells.—M. O. L.

**Tissue respiration and endocrine function. IV. Influence of thyroidectomy on succinoxidase activity of surviving tissues.** Dye, J. A. and G. H. Maughan, *Proc. Soc. Exper. Biol. & Med.* 26: 441. 1929.

Muscle tissue from thyroidectomized pups showed a diminution of 16 per cent as compared with normal controls in the power to oxidize succinic acid.  
—M. O. L.

**Occurrence of asthma in patients manifesting evidences of thyroid dysfunction.** Elliott, C. A., *Am. J. Surg.* 7: 33. 1929.

The coincidence of asthma with hypothyroidism in one case and hyperthyroidism in 5 cases is reported. The clinical observations suggest, but do not demonstrate, in the author's opinion, that a physiological relationship may exist between asthma and hyperthyroidism. Their coexistence may be merely casual. The fact that but 6 patients thus afflicted have been seen in this clinic during the past 11 years would tend to support the latter view. Since 2 of these patients have been definitely relieved of asthma and hyperthyroidism by thyroidectomy and clearing up of definite focal infections, such a procedure seems warranted as a method of treatment. Adrenalin relieved 4 temporarily of asthma while hyperthyroid, although one had a frightful general reaction. Adrenalin relieved 2 of asthmatic attacks during periods in which they were definitely hypothyroid. Iodine had a beneficial effect on the asthma in one patient, who was continuously hypothyroid, but no conclusion can be drawn as to the effect of the iodine alone on the asthma of the others, although it was given to all of them, and the thyroid status of 4, while definitely hyperthyroid, seemed improved thereby.—R. G. H.

**Quantitative observations on thyroxine and allied substances. II. Effects on the oxygen consumption of rats.** Gaddum, J. H., *J. Physiol.* 68: 383. 1930.

The technique is described in detail. Mean consumption was 14.44 cc. O<sub>2</sub> per kgm. per min. (.00700 cal. per sq. m. per 24 hrs.). The most effective method of administration of thyroxine was found to be subcutaneous injection of alkaline water solution. The response was decreased after thyroidectomy and increased after a previous injection, l-thyroxine being more effective than d-thyroxine. Thyreoglobulin was more effective than thyroxine when given orally. Subcutaneous injection gave responses proportional to the respective iodine contents. Two dipeptides containing thyroxine, n-acetylthyroxine, l-acetylthyroxine, diiodothyronine were all effective. Replacement of the iodine with bromine gave a substance slightly effective. Thyronine, thyroxamine, diiodotyrosine and B-dialanine were ineffective.—C. I. R.

**Thyrotoxicosis in childhood.** Ginsburg, S., *Am. J. Dis. Child.* 37: 922. 1929.

This condition is not as rare in children as formerly supposed, and while its course is milder and more atypical than in the adult, it may run an acute course with a fatal termination. The paper is a plea for the use of radium in preference to surgical intervention in toxic goiter. In the differentiation between the simple and toxic types of goiter, the author employs two tests: the iodine and radium therapeutic tests. Iodine either ameliorates or aggravates the symptoms of exophthalmic goiter or of toxic adenoma, but it rarely affects simple goiter. In the latter type, there is rarely any constitutional effect, even

with marked shrinkage of the thyroid gland. The application of radium is followed by an improvement in toxic cases, but not in simple goiter, asthenia or neuro-circulatory conditions.—M. B. G.

Influence of the thyroid on blockage of the reticulo-endothelial system (Influence de la thyroïde sur le blocage du système réticulo-endothélial).

A new method for measuring the activity of thyroid preparations (Nouveau mode de détermination des préparations thyroïdiennes). Goebel, F., *Compt. rend. Soc. de biol.* 101: 596. 1929.

In normal dogs injections of colloidal silver, in sufficient amounts to cause blockage of the endothelial system, produces a hypoglycemia and a reduction in cholestérine. In thyroidless dogs injections of silver cause no such reduction. Thyroidless dogs fed thyroid for a period respond as do normal dogs. This result of thyroidectomy may be due to (1) a reduction in the phagocytic activity of the endothelium, (2) a reduction in the tonus of the sympathetic system, or (3) increased glycogen fixation in the liver. The activity of thyroid preparations may be gauged by testing their ability to restore the normal blocking and resultant hypoglycemia in thyroidless dogs.—J. C. D.

Effect of feeding small doses of potassium iodide on the thyroid gland. Gray, S. H. and J. Rabinovitch, *Proc. Soc. Exper. Biol. & Med.* 26: 468. 1929.

The daily feeding of 0.0001 gm. KI to guinea pigs did not increase the number of mitoses and did not affect the structure of the thyroid gland. Feeding daily 0.0001 gm. KI to guinea pigs produced only a slight increase in mitoses, but at the same time produced an otherwise histologically active thyroid gland. The feeding of 0.01 gm. KI stimulated the thyroid in all its histological phases.—M. O. L.

Pathogenic basis for iodine treatment in thyrotoxicosis. Holst, J., *Norsk. Mag. of Laegevidensk.* 99: 973. 1929. *Abst., J. A. M. A.* 93: 1516.

Holst treats of the action of iodine in primary thyrotoxicosis (exophthalmic goiter) and considers the changes in the blood and goiter produced by the iodine treatment of thyrotoxicosis according to Plummer. The thyroid has two functions, as follows: (1) the production of the secretion and (2) the storage of the secretion and the regulation of its discharge. Administration of inorganic iodine is believed to arrest the "thyroid diarrhea" or rapid discharge of the thyroid secretion into the blood in thyrotoxicosis. The relation between the inorganic iodine in the blood and the capacity of the thyroid to retain its secretion, called the "intermediary iodine balance," is discussed.

Effect of thyroid administration on protein and fat metabolism (Über den Einfluss von Schilddrüsendarreichung auf den Eiweiss- und Fettstoffwechsel). Kommerell, B., *Biochem. Ztschr.* 208: 112. 1929.

A dog was subjected to a fasting period of 18 days, a rest period of five weeks, and then another fasting period of 17 days. During the second fast period thyroid (5 grams Gland. thy. Merck) was given daily. Daily studies were made during both periods of the nitrogenous equilibrium and of the basal metabolism. From these data the percentages of protein and fat consumed were calculated. Thyroid administration led to an increase of 30.5% in the basal metabolic rate, 31.3% of which was attributed to the combustion of protein, 68.7% to the combustion of fat: the nitrogen output was doubled. Complete tables and graphs are given, as well as description of some modifications of the Haldane gas analytical method.—B. S. Walker.

Action of the thyroid gland on proteins (La fonction protéocrasique du corps thyroïde). Loeper, M., A. Lemaire and J. Tonnet, *Compt. rend. Soc. de biol.* 102: 279. 1929.

Blood in the thyroid arteries and veins of dogs and horses was studied. The nucleo albumin was much decreased, the serine increased, the sulphur left after precipitation of the albumins was increased, and the amino acids reduced by passage of the blood through the gland. The total blood albumin remained unchanged. Similar results followed when thyroid extract was added to blood in vitro.—J. C. D.

Experimental researches on heredity of thyroid conditions (*Recherches expérimentales sur l'hérédité thyroïdienne*). Marza-Rusnac, E., *Rev. franç. d'endocrinol.* 7: 320. 1929.

In guinea pigs thyroidectomy of the parents results in a lessening of the size and weight of the thyroid of the new born. The offspring of hyperthyroidised animals are weaklings, whose weight at birth is less than that of controls.—J. Gagnon.

The sedimentation velocity of erythrocytes in thyrotoxicosis. Mora, J. M. and J. T. Gault, *J. Lab. & Clin. Med.* 15: 590. 1930.

The sedimentation speed of erythrocytes was studied in 30 cases of thyrotoxicosis, by the Linzenmeyer method, before and after thyroidectomy. The rate was increased in all cases before operation. The administration of iodine decreased the speed of sedimentation in 6 out of 11 cases, and increased it in 5 cases. Thyroidectomy was followed by an increased rate in 13 cases, and by a decreased speed in 14 cases. There seemed to be little parallelism between the sedimentation velocity, the basal metabolic rate, and the clinical picture.—Authors' Summary.

Studies on the behavior of cholesterol within the animal body. IV. The rôle of thyroid gland in the content of cholesterol in each organ and tissue. Onizawa, J., *J. Biochem.* 10: 425. 1929.

Analysis was made of tissues for free and ester cholesterol in rabbits with thyroids removed, similar animals with adrenalin injection; also in animals fed thyroid, and the same plus adrenalin injection. Full results are given in tabular form. Following thyroid removal, ester cholesterol is increased in plasma and adrenals. Adrenalin injections lead to an increase in free cholesterol in the tissues, whether or not thyroid be present.—B. S. Walker.

An inquiry into the fate of thyroxin in the treatment of nephrosis. Platt, R., *Quart. J. Med.* 23: 129. 1929.

Patients with chronic nephrosis have an extraordinary tolerance to thyroxine given either orally or intravenously. This is not due to rapid excretion of thyroxin by the kidney. It is therefore presumed that thyroxin is either rapidly destroyed in the body, or its action inhibited, but it is suggested that such an inhibition does not depend upon the increased level of the blood cholesterol which is commonly found in these cases.—E. C. Kendall.

Effect of infections on the thyroid gland. Rabinovitch, J and S. H. Gray, *Proc. Soc. Exper. Biol. & Med.* 26: 472. 1929.

In 22 guinea pigs an acute and chronic peritonitis was induced by injecting fecal material intraperitoneally. In only one guinea pig examined before death was any desquamation of epithelium and softening of the colloid in the thyroid gland noted. In guinea pigs found dead, post mortem desquamation occurred earlier in experimental infections than in controls. In chronic infections, the guinea pig thyroid presented no deviations from the normal.—M. O. L.

The thyroid gland of sheep according to breed, age, sex and season (*Die Abhängigkeit der Schilddrüsenausbildung von Rasse, Alter, Geschlecht und Jahreszeit bei verschiedenen Schafrassen*). Spöttel, W., *Ztschr. f. Anat. p. Entwicklsg.* 89: 606. 1929.

The relative weight of the thyroid varies greatly in different breeds. In general the male has a larger thyroid than the female. The effect of castration varies with age and breed. The effect of pregnancy is also variable—the gland usually becomes darker in color and more pulpy in consistency. The thyroid is only about half as large in summer as in winter. The histological structure is described in these various conditions. In the spring, especially in March, there is evidence of follicular degeneration. The histological structure of the epithelium indicates greater secretory activity in the winter than in the summer. The method of formation of new follicles is described. The seasonal variation in secretory activity is apparently largely due to tempera-

ture changes, although seasonal variations, especially in light and food, may be contributing factors. The hypofunction of the thyroid beginning in the spring and the hyperfunction which commences in the fall are probably factors in regulating the growth of wool. These and other observations on the sheep are compared with those reported for other animals.—A. T. R.

**Exophthalmic goiter.** Thompson, W. O. and Bernice Alexander, *Arch. Int. Med.* 45: 122. 1930.

In tests on 15 subjects, it was found that the concentration of protein in the cerebrospinal fluid was within the lower limits of normal in most cases of exophthalmic goiter, and usually showed a well marked increase, in association with a gain in weight and reduction in basal metabolism, following a subtotal thyroidectomy.—R. G. H.

**The range of effective iodine dosage in exophthalmic goiter.** Thompson, W. O., A. G. Brailey, Phebe K. Thompson and E. G. Thorp, *Arch. Int. Med.* 45: 261. 1930.

During the daily administration of 1 drop of compound solution of iodine (about 6 mgm. of iodine) to 17 unselected hospital patients with exophthalmic goiter, 15 showed a reduction of 15 to 49 points in basal metabolism, and 2 showed no change. The reduction appeared to be as great as that noted by other observers on much larger doses. A maximum decrease in basal metabolism also appeared to occur in most out-patients during the administration of 1 drop daily. In the house patients, the administration of 1 drop daily caused a maximum reduction in basal metabolism in 7 days on the average. The time that elapsed between the beginning of iodine administration and the onset of a decrease in basal metabolism varied from one to four days. In 5 of the cases it had started within 24 hours after administering only 6 mgm. of iodine. The doses of iodine used at present in the routine pre-operative and post-operative treatment for exophthalmic goiter are probably needlessly large. It is doubtful if more than 5 drops of compound solution of iodine daily is ever necessary to produce a maximum effect. In comparing the effects of various doses of iodine, it is essential to secure a resting level of basal metabolism before medication is begun.—Authors' Summary.

**The range of effective iodine dosage in exophthalmic goiter. II. The effect on basal metabolism of the daily administration of one-half drop of compound solution of iodine.** Thompson, W. O., E. G. Thorp, Phebe K. Thompson and A. C. Cohen, *Arch. Int. Med.* 45: 420. 1930.

During the administration of  $\frac{1}{2}$  drop of compound solution of iodine (3 mgm. of iodine) daily to twenty unselected hospital patients with exophthalmic goiter, thirteen showed a significant reduction in basal metabolism, five showed no change and two showed an increase. Seven showed a lower level of basal metabolism during the subsequent administration of 30 drops daily than during the administration of  $\frac{1}{2}$  drop daily. The average reduction in basal metabolism during the administration of  $\frac{1}{2}$  drop of compound solution of iodine daily was 14 points (from plus 40 to plus 26 per cent)—which was only about half as great as that during the administration of 1 drop daily. The total decrease in metabolism from all doses of iodine was less than in the 1 drop series. In the thirteen cases that responded, the maximum reduction in basal metabolic rate appeared on the average in seven days. In four cases a reduction occurred within twenty-four hours. The daily oral administration of 3 mgm. of iodine in the form of compound solution of iodine is inadequate to produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston, whereas 6 mgm. is adequate.

—Authors' Summary.

**Studies in reactions of simple goiter to iodine.** Webster, B., *Bull. Johns Hopkins Hosp.* 45: 215. 1929.

Potassium iodide in quantities of 5, 2.5 and 1.25 mgm. was injected intraperitoneally into rabbits with simple goiter (struma diffusa parenchymatosa type) and the changes in heat production were studied and correlated with

the histological changes produced in the gland, as determined by biopsy. The quantity of thyroid hormone elaborated, as indicated by changes in heat production, appeared to vary directly, within certain limits, with the amount of available iodine, as did the extent of involution produced in the gland. This relationship apparently held true until involution was nearly complete. A possible explanation for this phenomenon is suggested.—Author's Abstract.

**Lymphadenoid goiter and its clinical significance.** Williamson, G. S. and I. H. Pearce, with a note on its etiology in rats by R. McCarrison, *Brit. M. J.* 1: 4. 1929.

Histological evidence suggested that the thyroid had 2 functions, (1) the production of the secretion proper (lymphogenic function) and (2) the accumulation of Iodo-colloid. The normal secretory process causes reticulo-endothelial activity of the thyroid as well as an increase of lymphocytes in the inter-follicular lymph spaces (lymphogenic secretion). Disturbances of this function give rise to lymphadenoid goiter in which lymphocytes infiltrate the thyroid lymph spaces. Later parenchymal hyperplasia results in the formation of islands of solid epithelial tissue in the follicular spaces. As the process advances the lymphocytic infiltration becomes diffuse and little colloid is present. Atrophy follows exhaustion of the glandular epithelium. At the same time fibrosis of the reticulo-endothelial tissue gives rise to fibrous whorls. Ultimately the "woody" thyroid or the gland of myxoedema may result. Thyroid lymphogenesis is the cause of gland atrophy and a progressive hypothyroidism, but is essentially due to a disturbance of lymphogenic function of the gland.

—Wm. Susman.

**The importance of the thyroid gland for the nervous activity of animals.** Zavadovsky, B., *Am. J. Physiol.* 90: 567. 1929.

Hyperthyroidisation with large single doses in chickens and in dogs revealed a double phased action—degradation and disappearance of the conditioned reflexes in the first days after feeding with thyroid gland, and increase of nervous excitability and return of the conditioned indices beginning with the third to fifth day. When fed with small doses of the thyroid gland daily a general increase of the conditioned indices was observed whereas all the reactions become more exact, including the differentiation reaction. Simultaneous study of the unconditioned salivary secretion did not allow interpreting the effect of the experiments as a mere increase of excitability of the peripheral apparatus of the salivary gland but indicated some immediate changes in the activity of the brain cortex brought about by hyperthyroidism. In two dogs with fully established conditioned salivary reflexes the thyroid glands were entirely removed and changes brought about in the conditioned reflex activity of the animals were systematically followed in the course of 8 or 9 months up to the death of the animals, which was caused by cachexia. A sharp decrease of the reflex indices was noted together with a lengthening of the latent period and diminution in the quantity of the secreted saliva; all these changes began on the second month after the operation and reached about 50% of their initial value.—M. O. L.

**The influence of the acetyl derivative of thyroxin on moulting and decolorization of hens' feathers** (Über den Einfluss der Azetylderivate des Thyroxins auf die Mauser und Depigmentierung des Hühnergefieders). Zawadowsky, B., A. Titajeff and S. Faiermark, *Endokrinol.* 5: 416. 1929.

The purpose of the experiment was to determine which parts of the thyroxin molecule caused the moulting and decolorization of feathers which the authors had, in an earlier series of experiments, shown to be a result of administration of the thyroid hormone. The substances tested were the original (keto) form of thyroxin, the open-ring form, and the acetyl derivatives of both of these compounds. Injections of alkaline solutions of the four substances were given subcutaneously to black hens. In the case of the keto and open-ring forms, and the acetyl derivative of the latter, injections were followed first by moulting, and later by growth of white feathers in the region around the site of the injection. The acetyl derivative of the keto form pro-

duced but little effect. Diiodotyrosin, given in large doses, had no effect. The authors discuss especially the slight reaction of the hens to acetyl derivative of the keto form. They compare the effect this has on the plumage of hens with amphibian metamorphosis on the one hand and metabolic changes on the other, apparently regarding all three reactions as essentially similar. Since this form of acetyl thyroxin accelerates amphibian metamorphosis, produces but little change in plumage, and has no effect on the metabolic rate in mammals, they conclude that birds stand midway between amphibia and mammals in the type of iodine compounds to which they respond. They suggest that the effect on plumage may be used as a test in comparative studies of thyroxin and its derivatives.—M. M. H.

**A biological method for estimation of thyroid activity (Eine biologische Methode zur Bestimmung der Schilddrüsen-Aktivität bei Tieren).** Zawadovsky, B. and M. Nowikova, *Endokrinol.* 1: 167. 1928.

A research was carried out on 107 Axolotls in which were implanted grafts of thyroid from chickens, dogs, cats, rabbits, guinea-pigs and doves. This method permits an evaluation of the efficacy of the thyroid tissue in terms of its metamorphosis-inducing properties. It was found that 30 mgm. was the minimal and 50 mgm. the optimal dosage for Axolotls weighing 4-10 grams. Thyroid tissue from various species proved to be about equally efficacious, that from hens had greatest potency.—R. G. H.

# ENDOCRINOLOGY

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## ENDOCRINOLOGY AND NEUROLOGY\*

PETER BASSOE, M.D.  
CHICAGO, ILL.

Fellow members and guests of the Association for the Study of Internal Secretions: Our fourteenth annual meeting opens under auspicious circumstances. We are assembled in a city in the center of the continent, an important center for research in the field of endocrinology and for the manufacture and distribution of endocrine products. Here in Detroit we can not only listen to accounts of work done, ask questions and utter criticisms, but we may visit able investigators in their laboratories and witness precise manufacturing technique based upon the investigations of these scientists. This location is ideal also for the exchange of ideas between the two largest nations on this continent. We of the United States owe an expression of homage, admiration and gratitude to our neighbors on the north, who within a period of a few years have given insulin and parathyroid hormone to the world. However, we may permit ourselves to point with some pride to recent achievements in connection with the hypophysis, thyroid, adrenals and gonads. That our Association, its annual meetings and its journal are growing in importance and commanding increasing serious attention and confidence is apparent. As a sign of growth I call your attention to the size and scope of the program of this meeting, and I am confident that its high quality will speak for itself. This is the first time that your officers have ventured to invite you to spend two days at our meeting, and they have done so with the conviction that it is justified by the quantity and quality of new research to be presented.

The one ironical and malapropos feature of this meeting is the fact that its presiding officer is the only participant in the program who is devoid of distinction as an investigator in the field which this Association represents. At previous meetings he has never been more than an humble but interested listener, who always has felt amply rewarded by information acquired which has helped him in his daily work as a practitioner and teacher of neurology. The close interrelationship between endocrinology and neurology has been personified in three of his predecessors. Barker, Cushing and Timme, all of whom, unlike the present incumbent, have made important contributions in both fields.

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\*President's Address at the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Mich., June 23, 1930.



Neurologists are often, and sometimes justly, accused of being speculative, verbose, and afflicted with a cumbersome nomenclature, but they must be given credit for having early understood the importance of the part played by the organs of internal secretion. Long ago the neurologist, Wagner-Jauregg of Vienna, said that organotherapy is not only a field for research but should itself be a means of research. An example is the amazing production of many nervous and mental syndromes by insulin reactions. Many a neurologist unfamiliar with these reactions has seen his reputation suffer on account of his failure to keep abreast of the progress of endocrine therapy. Psychiatrists are grateful to the discoverers of insulin because they find it a useful drug for undernourished, depressed patients. The permanent benefit from insulin in such cases makes up many fold for the occasional production of transient nervous and mental symptoms in diabetics. Without knowledge of the action of insulin we should not have learnt to understand the pathogenesis of convulsions and coma in cases of adenoma of the islands of Langerhans. Thus, we here have seen Wagner-Jauregg's prophecy come true. A few years ago it began to look as if it were going to be admitted that the endoerines regulated everything from menses and hibernation to personality, poetry and politics. However, a reaction has come, and now two or three new regulating centers in the hypothalamic region are being discovered (or imagined), for every new hormone. Mauthner's old idea of a sleep center has been revived. Thirst, diuresis, adiposity and emaciation are made and unmade by manipulating the hypothalamus regardless of the hypophysis, both in its absence and in its presence. Centers controlling not only water, sugar and fat metabolism but protein metabolism and basal metabolism are now described by physiologists. I shall confine myself to pointing out briefly some of the contributions of neuropathology and clinical neurology to these problems. Observations on epidemic encephalitis, particularly its chronic forms, have taught us that lesions of the brain may cause many symptoms and syndromes formerly considered due only to lesions of the hypophysis, notably diabetes insipidus and adiposis with genital atrophy. However, detailed anatomic investigations are still few. Felix Stern (1) observed adiposis in 39 of 500 cases and attributes it to lesions of the tuber cinereum. It is noteworthy that he occasionally observed regression of both the adiposis and genital atrophy. Pubertas praecox, preceded by salivation and parkinsonism, has been described by Stern (2), John (3) and Wimmer (4). The frequency of hyperidrosis and increased sebaceous secretion ("greasy face," "Salbengesicht") in encephalitis is of interest in connection with Lotmar's idea of a sweat center in the posterior medial portion of the thalamus and L. R. Müller and Greving's center for sebaceous secretion in the tuber cinereum. Riese (5) observed a young woman with encephalitic rigidity, obesity, considerable sexual excitement and colostrum-like secretion from the breasts which had been present over five years. He ascribes this to disorder of vegetative brain centers. Increased basal metabolic rate is fairly common both in chronic parkinsonian encephalitis and in true paralysis

agitans. One of the largest groups of patients tested is that reported by Naccarati (6). Of 47 chronic encephalitic patients 28 showed altered rate, 25 increased, 3 decreased. There was no relationship between the degree and extent of tremor and the basal rate, which is an argument against the theory that increased muscular activity is the cause of increase in basal rate. Extensive animal experiments over a period of years by Steinhaus (7) also failed to support the muscular theory. Other explanations offered are that actual activation of the thyroid occurs or that a certain center in the interbrain is affected by the pathologic process. Gräfe and Grünthal (8) have performed experiments on dogs which led them to believe that basal metabolism is regulated by centers in the interbrain independent of the heat center. When they injected silver nitrate solution into the posterior portion of the interbrain basal metabolism was lowered.

Neurologists now frequently see patients with parkinsonian tremor with increased metabolic rate who have had thyroidectomy with little or no benefit. I shall briefly relate some of my own experience with cases offering problems as to the parts played by head trauma, encephalitic virus, the thyroid and the hypophysis.

#### CASE REPORTS

CASE 1. A woman 52 years old, previously healthy, on Feb. 9, 1926, struck her head against the top of a taxicab and was dazed for a few moments. She had severe pain on the left side of the forehead and at the occiput, which kept her awake during the night. The next day she noticed a tremor in the right arm and a few days later, in the jaw and right leg. The pain subsided in a few weeks but the tremor persisted. Before the accident her weight was 229 pounds. When first seen by me on July 15, 1926, her weight was 179 pounds. There was a constant tremor of parkinsonian type in the right arm and much of the time a similar tremor in the right leg and jaw. This tremor was suppressed by voluntary movement. She did not swing the right arm in walking. There was no visible thyroid enlargement and the basal metabolic rate was +1. The pulse rate during three days of observation at this time ranged from 80 to 110. The condition remained about the same for the next three months, during which time she had frequent and profuse nose-bleed. In November the pulse rate became more rapid and on December 3 the basal metabolic rate was +73 and four days later after continuous rest in bed it was +48. The pulse rate ranged from 80 to 130 and was usually above 100. After a few weeks on Lugol's solution the basal rate was +1 on January 27, 1927, but on May 21 it was +38, at which time the weight was 161 pounds. During a stay of 12 days in the hospital at this time the pulse rate was usually below 100. The tremor was less marked and involved chiefly the lower jaw. No further examination has been made, but in the latter part of May, 1930, the patient states that she still has tremor, but is able to work in a store and that she has had no more basal tests. I gave the opinion that the head injury had brought on the paralysis agitans syndrome. If this is true it may also be true that changes in vegetative brain centers later brought on the hyperthyroid syndrome.

CASE 2. A married woman 28 years old, mother of two children, was seen on March 11, 1929, on account of a parkinsonian tremor of the left hand which had been present for a year. There was also at times a tremor of slower rate in the left foot. During the preceding three years her weight had gradually increased from 140 to 197 pounds. There was no history of an acute attack of encephalitis. During the following months she began to lose weight and the pulse rate became more rapid. On April 22, her weight was 176 pounds, basal rate +38. The spinal fluid was normal. The serum calcium was 10.9. The tremor was partially controlled by hyoscin. On November 5 the weight was 159 pounds, basal rate +20. Lugol's solution was given for several weeks, but on February 27, 1930, the weight was 143 pounds and the basal rate +35. The

pulse rate became more rapid. On April 22, her weight was 176 pounds, basal rate +38. Since then the patient has been taking hyoscin, has gained a little in weight and improved in strength. The tremor is less marked but remains typically parkinsonian. The thyroid gland is not enlarged. It is thought that this is a case of chronic epidemic encephalitis and that the obesity, tremor, and subsequent loss in weight and increased metabolic rate are the results of disease involving brain centers rather than endocrine glands.

If time permitted I might cite numerous cases of true paralysis agitans with increased metabolic rate and with and without thyroid enlargement and in which thyroidectomy has been of dubious value. I might tell of young encephalitic patients with combinations of many kinds. Thus, a man of 23 years, who gave a history of an acute illness with diplopia at 18; became obese, drowsy, had upward spasms of the eyeballs and athetoid movements of the left hand. His weight was 197 pounds, blood pressure 164, pulse rate 70, and basal metabolism +26.

Another interesting syndrome with similar problems is symmetrical lipomatosis, which may appear or be suddenly aggravated in connection with mental and nervous phenomena. This condition is undoubtedly related to, in fact may merge into, the so-called adiposis dolorosa, which, however, is itself scarcely a clinical entity.

CASE 3. A woman, 52 years old, whose aunt had lipomas, was seen in December, 1929, during a depressive, confusional psychosis, without signs of organic brain disease. She had had multiple lipomas for years, but during the psychosis they had rapidly increased in number, size and tension. They were located about the neck, upper back and arms. The basal metabolism was -13. However, she grew worse on thyroid and developed attacks of rapid breathing. Curiously enough, when her physician, Dr. Leslie Rutherford of Peoria, substituted Lugol's solution, a rapid improvement in mental symptoms and reduction in the size of the lipomas set in.

CASE 4. A professional man of 30 years, first seen last February through the courtesy of Dr. Woodyatt, had been gaining weight for four years, complained of thirst and increased diuresis for four months, during which time he also showed a mild mental disturbance, especially in the line of being talkative and hailing strangers on the street. Last December symmetrical lumps appeared over the zygomas and on the neck. The skin over them appeared edematous and red and the patient complained that these areas felt very hot. Last January sugar was found in the urine and glycosuria still persists. It can be controlled by insulin but the polyuria remains and requires pituitrin. Leucocytosis is persistent, the latest count, on June 18th, being 19,300. One of the lumps on the neck was excised and was found to consist only of fat. Visual fields, sella roentgenograms and basal metabolic rate were normal. Ataxia of the left arm was present early and followed by slight, but definite, weakness of the left arm. Otherwise motor and sensory condition and reflexes have been normal. To my mind a case of this kind is better explained by an encephalitic lesion in the interbrain, affecting vegetative centers, or by a functional disorder of these centers, than by any primary affection of the hypophysis or other endocrines.

We might discuss the endocrine features of muscular dystrophy, generalized neurofibromatosis and many other obscure conditions, but I do not wish to waste your time with speculations. For the same reason I shall dismiss the huge field of the relationship of endocrinology to psychiatry with the statement that there are so many unknown factors in both of these sciences that few conclusions can be drawn. Study of endocrine conditions in definite psychoses, of psychic conditions in definitely demonstrated endocrine disorders, and of psychic reactions to administration of endocrine

preparations containing known hormones are three of the roads which may lead us to more knowledge.

Once more I wish to express my regret that, unlike my predecessors, I cannot give you any account of research work. I can only make a plea for continued cooperation between workers in the fields of endocrinology and neurology and express the hope and conviction that future research on the vegetative nervous system, and particularly on the intracranial part of it, will bring significant results.

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# THE ACTION OF PITUITRIN, PITRESSIN AND PITOCIN ON THE BLOOD PHOSPHATIDES

W. RAAB,\* M.D.

From the Department of Physiology, Harvard Medical School  
BOSTON

The posterior pituitary hormone, pituitrin, exerts some characteristic effects on fat-metabolism and seems to be an important factor in the consumption and distribution of body fat. These facts were demonstrated experimentally for the first time in 1925 by Coope and Chamberlain (6), who found a considerable accumulation of fatty acids within the liver under the influence of pituitrin and by Raab's (14) studies on the changes of blood fat and blood acetone bodies through various hormone preparations. Pituitrin was the only one that produced a marked and comparatively long lasting action on the blood fat level—a regular decrease during several hours. For obtaining this effect in fasting dogs large doses of pituitrin are needed if injected subcutaneously, while the same effect can be produced by very small doses (0.18 cc.) if injected into the third ventricle of the brain. The pituitrin effect is abolished by destruction of the tuber cinereum at the base of the mesencephalon, by paralyzing the mesencephalic centers with drugs (acetyl-salicylic acid, etc.), by transection of the cervical spinal cord, by section of the splanchnic and by paralyzing the sympathetic nervous endings with ergotamin. Hence pituitrin appears to act on the fat metabolism through a nervous path starting in the midbrain and ending with the splanchnics. The fat disappearing from the blood stream is accumulated and probably subsequently destroyed in the liver. (Clinical cases of both hypophyseal and cerebral type of obesity may, therefore, probably be considered as due to a disturbance of the function of the so-called "hypophysis-mesencephalon system" as far as its stimulating effect on fat destruction is concerned.) Raab's (14) first experiments were based on the determination of the total petroleum-ether fraction (containing neutral fat plus free cholesterol). Later on Blix and Ohlin (1) and Raab (14) stated that the effect of pituitrin results merely in a decrease of neutral fat while the cholesterol remains practically unaltered. The acetone bodies of the blood show a slight fall (Raab, 14). The findings of Coope and Chamberlain (6) (increased fat absorption by the liver), although not confirmed by van Dyke (7), have been corroborated recently by Oshima (13) and by Steppuhn, Timofejewa and Ljubowzowa (15). The latter found also a corresponding loss of fat in the peripheral tissues but do not believe in a destruction of fat within the liver because the amounts of fat in the liver, as well as in the tissues, return again towards the normal after some time. Yet the total fat content of the body seems to be diminished by pituitrin.

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\*Research Fellow of the Rockefeller Foundation.

Blix and Ohlin (1) observed that pituitrin decreased the blood phosphatides even more than neutral fat and emphasize the important rôle of the phosphatides in the intermediary metabolism of fat which has also been pointed out by Bloor (3), Jost (9) and others.

Recently, there have been carried out most interesting experiments on the effect of total sympathectomy by Cannon and his collaborators (4). The close relationship between the action of pituitrin on blood fat and the sympathetic nervous system shown by Raab led Dr. Cannon to suggest experiments with pituitrin on sympathectomized dogs. Two of his operated animals were kindly placed at my disposal. Because of Blix and Ohlin's statement of a particularly strong action of pituitrin on the blood phosphatides I decided to use this effect as a test and to employ for the determination of lipid-phosphorus in the blood (alcohol-ether extract after Bloor) the method of Fiske and Subba Row (8), the accuracy of which has been confirmed by various authors.

Furthermore, it seemed of some interest to examine the two pituitrin constituents, pitressin and pitocin, which have been isolated lately by Kamm and his collaborators (10).

All experiments have been made on dogs (8 to 20 kgm.) fasting for approximately sixteen hours. No food or water was given during the experiments. Blood samples of 2.5 cc. were taken from a hind leg vein. Pituitrin, pitocin and pitressin (all Parke, Davis & Co.) were injected subcutaneously. Except for stimulation of bowel movements there was not observed any conspicuous alteration of the animal's general behavior after the injections. The doses given varied between 6 and 12 cc. (mostly 12cc.). In their specific activity on blood pressure and tone of the uterus 1 cc. pitressin corresponds to 2cc. of pituitrin and 1cc. pitocin corresponds to 1 cc. of pituitrin (personal information by Dr. Kamm).

## RESULTS

(a.) *Control experiments* (fasting): The lipid phosphorus showed considerable irregularities, rises and falls varying in amounts from +21.8 to -13.7 per cent of the initial figure (on an average from +6.2 to -3.9 per cent). See Table I.

(b.) *Pituitrin*: Doses of on an average 21 cc. (injected at once) caused in all of ten experiments a moderate drop of the lipid phosphorus varying in degree from -4.2 to -29.1 per cent (on an average -14.6 per cent). One single rise of 1.6 per cent above the initial level in the third hour can be considered as insignificant. See Table II.

(c.) *Pituitrin in sympathectomized dogs*: The effect was not uniform. There occurred rises up to +13.8 per cent, while the decreases attained a maximum of only -15.6 per cent (on an average -6.7 per cent). See Table III.

TABLE I  
CONTROL EXPERIMENTS  
(FASTING DOGS)

Body Weight in kgm.	Blood Lipoid Phosphorus (in mgm. %)						Maximal Differences (within 12 hours)	
	Time in Hours							
	0	3	6	9	12	24	+	-
14	14.6	14.1	13.8	14.3	13.8	14.6	....	5.4%
20	12.1	10.5	11.9	12.2	10.8	11.3	....	13.2%
20	13.4	13.0	13.0	14.8	15.2	15.5	13.0%	3.3%
20	13.0	13.5	12.3	12.9	11.2	11.3	3.4%	13.7%
14	14.4	14.3	14.2	14.4	....	14.2	0.3%	1.0%
14	11.0	12.4	12.5	11.7	12.0	9.2	13.5%	....
20	11.0	9.9	10.3	....	10.7	10.5	....	9.9%
9	11.9	10.4	12.0	14.5	14.2	12.0	21.8%	12.2%
17	13.0	12.1	13.2	12.7	12.8	12.6	1.1%	6.8%
12	13.0	12.2	14.2	14.2	13.0	13.1	9.2%	6.1%
Average:	12.7	12.2	12.7	13.5	12.6	12.4	6.2%	3.9%

TABLE II  
PITUITRIN IN NORMAL DOGS

Body Weight in kgm.	Pituitrin	Blood Lipoid Phosphorus (in mgm. %)						Maximal Differences (within 12 hours)	
		Time in Hours							
		0	3	6	9	12	24	+	-
14	6 cc.	11.7	11.5	10.5	10.4	10.4	10.5	....	11.0%
14	2x10 cc.	11.4	10.5	10.4	10.2	10.2	10.4	....	10.9%
8	12 cc.	12.0	9.3	10.1	9.5	9.8	10.9	....	22.5%
20	12 cc.	10.7	9.7	8.4	9.7	10.1	10.1	....	21.4%
14	12 cc.	14.3	11.5	13.7	13.6	....	13.1	....	19.2%
16	12 cc.	13.3	12.7	12.3	12.5	....	13.6	....	7.5%
20	12 cc.	13.0	13.0	11.6	12.5	11.8	14.5	....	11.1%
20	12 cc.	15.0	15.3	14.4	14.6	14.6	14.6	1.6%	4.2%
17	12 cc.	16.5	14.2	....	13.8	13.6	16.3	....	17.5%
12	12 cc.	12.3	12.4	8.7	12.3	10.2	13.8	....	29.1%
Average:		13.0	12.0	11.1	11.9	11.3	12.8	....	14.6%

**TABLE III**  
**PITUITRIN IN SYMPATHIECTOMIZED DOGS**

Body Weight in kgm.	Pituitrin	Blood Lipoid Phosphorus (in mgm. %)						Maximal Differences (within 12 hours)	
		Time in Hours						+	-
		0	3	6	9	12	24		
16	12 cc.	12.5	12.0	10.7	11.4	10.6	10.9	....	15.2%
10	12 cc.	10.5	11.0	11.0	11.1	11.1	11.5	13.8%	....
16	12 cc.	14.0	14.0	13.5	13.7	13.7	11.9	....	7.2%
16	12 cc.	10.8	9.8	10.7	12.2	11.6	11.6	12.0%	9.2%
10	12 cc.	11.1	10.5	10.0	9.7	10.2	10.6	....	12.1%
10	12 cc.	11.3	10.5	10.6	10.6	10.5	10.3	....	7.1%
17	10 cc.	12.0	10.7	11.5	11.7	11.9	11.5	....	11.2%
17	12 cc.	13.1	11.0	11.0	11.3	11.5	12.5	....	15.6%
10	12 cc.	10.8	10.6	10.6	10.3	10.7	10.8	....	4.6%
Average:		11.0	11.2	11.1	11.4	11.3	11.3	....	6.7%

**TABLE IV**  
**PITRESSIN IN NORMAL DOGS**

Body Weight in kgm.	Pitressin	Blood Lipoid Phosphorus (in mgm. %)						Maximal Differences (within 12 hours)	
		Time in Hours						+	-
		0	3	6	9	12	24		
14	6 cc.	11.1	10.4	10.7	....	10.5	10.4	....	6.2%
20	12 cc.	12.5	10.3	11.5	11.5	9.7	10.9	....	22.4%
17	12 cc.	14.6	14.6	15.2	15.3	14.5	15.8	4.7%	....
20	6 cc.	13.7	13.5	13.6	13.7	13.8	13.8	0.8%	1.1%
17	6 cc.	12.8	12.8	11.9	13.8	13.8	13.5	7.3%	7.0%
20	12 cc.	13.5	12.5	13.6	13.0	14.5	14.7	7.7%	7.4%
19	12 cc.	14.7	13.5	13.5	14.1	14.5	14.2	....	8.4%
18	12 cc.	11.6	11.5	11.3	10.8	11.1	10.8	....	6.8%
Average:		13.1	12.4	12.0	13.2	12.8	13.0	....	8.4%



(d.) *Pitressin*: There appeared no uniform effect. Rises went up to +7.7 per cent, falls down to -22.4 per cent. The average curve showed a fall to -8.0 per cent. See Table IV.

(e.) *Pitocin*: There occurred both rises and falls within a range from +17.9 to -31.8 per cent. The average curve showed a fall to -9.8 per cent. See Table V.

(f.) *Egg yolk intravenously*: No marked hyperlecithinemia was observed after the injections. As early as five minutes after the end of the injection the lipid phosphorus appears practically unchanged.

TABLE V  
PITOCIN IN NORMAL DOGS

Body Weight in kgm.	Pitocin	Blood Lipoid Phosphorus (in mgm. %)						Maximal Differences (within 12 hours)	
		Time in Hours						+	-
		0	3	6	9	12	24		
14	6 cc.	12.8	12.9	15.1	....	11.5	....	17.9%	10.5%
8	12 cc.	13.3	12.5	12.4	12.7	12.9	12.3	....	7.1%
19	12 cc.	13.8	12.6	12.7	12.4	12.0	13.1	....	13.3%
16	12 cc.	13.5	12.8	14.2	14.2	12.7	13.2	5.2%	5.5%
21	12 cc.	12.8	12.8	11.3	12.2	11.7	10.9	....	11.7%
17	12 cc.	12.8	13.7	12.8	13.0	....	13.5	7.0%	....
17	12 cc.	13.8	13.2	13.8	13.5	13.5	12.5	....	3.9%
12	12 cc.	13.5	12.7	12.8	12.0	9.2	11.1	....	31.8%
Average:		13.2	12.9	13.1	12.8	11.9	12.4	....	9.8%

#### DISCUSSION

The effect of pituitrin in decreasing the blood lipid phosphorus, although regularly present, was not as striking as had been expected with regard to Blix and Ohlin's (1) data concerning the blood phosphatides determined with Bang's method. This phenomenon is, therefore, not very suitable for use as a functional test, especially considering the frequent spontaneous decreases of lipid phosphorus values even in the control experiments. In contrast the petroleum-ether fraction and neutral fat usually increase during thirty hours fasting periods (Raab, 14). The cause of this quantitative discrepancy between Blix and Ohlin's and my own findings is not quite clear. Even the possible assumption of the presence of varying phosphorus-free substances within the "phosphatide fatty acids" determined after Bang-Blix would hardly explain the large difference between a maximum drop of 80 per cent (average 53 per cent) in Blix's and a maximum drop of only 29.1 per cent (average 14.5 per cent) in my experiments, although Blix (2) himself says: "As the nature of the phospho-

tides in the blood is unknown it is clear that the calculated phosphatide value by no means may be regarded as a real expression of the quantity of phosphatides actually present. Even if the phosphorus content of the blood phosphatides should be approximately the same it is not certain that the fatty acid content is the same (in lecithin and cephalin there are two molecules of fatty acid, in sphingomyelin probably one), and the phosphorus value thus besides tells very little about the quantity of fatty acids contained in the phosphatides." The preparation used was the same (Parke, Davis & Co.); the dosage it is true has been relatively somewhat smaller in some of my experiments, but not enough to give a satisfactory explanation. The type of previous diet as well as the species of animals may perhaps be of a certain importance for the quantitative results.

Attempts were made to produce an exogenous hyperlecithinemia for the purpose of testing the action of pituitrin on the artificially increased blood phospholipids. Oral feeding with lecithin does not produce any significant increase of the blood lipid phosphorus (Leites, 11), while Nerking (12) supposes (without, however, giving any experimental evidence for it), a long lasting retention of lecithin if injected into the blood stream, and Bloor (3) attributes the comparatively slow disappearance of fat from the blood after intravenous injection of egg yolk (0.6 to 0.8 gm. per kgm. body weight) to a retention by the presumably circulating lecithin which forms about 30 per cent of the egg yolk lipoids. My own experiments with intravenous injection of egg yolk (0.6 to 1.0 gm. per kgm. body weight) show that the phospholipids injected in this form disappear entirely from the blood within a few minutes and that it is not possible to produce a prolonged exogenous hyperlecithinemia by this means.

A complete absence of the pituitrin effect in the sympathectomized dogs cannot be claimed with certainty, yet in contrast to normal animals there occurred rises up to +13.8 per cent and the decreases both maximum and average were smaller than in normal animals. It might be mentioned that the bilateral removal of the thoracic and abdominal sympathetic had been done about one year before. The pituitrin effect was markedly weakened if not abolished in these completely sympathectomized animals.

The least enlightening results were obtained by the pitressin and pitocin experiments. Both of them led to rises and falls of the lipid phosphorus level, the latter being more frequent and more intense it is true. The decreases amounted to 22.4 per cent in the case of pitressin and to 31.8 per cent in the case of pitocin. It is, however, not possible to attribute the specific activity of the total pituitrin to one of the two fractions after these experiments, and it rather seems as if both of them may exert a certain influence. Determinations of their action on neutral fat will probably give clearer results.

In connection with the above mentioned facts concerning the influence of the hypophysis-mesencephalon system and of pituitrin on fat metabolism it seems justified to consider the intermediary and posterior lobe of

the pituitary as important factors in the maintenance of normal quantitative conditions of fat balance as a part of the internal body equilibrium or "homeostasis" (Cannon, 5).

#### SUMMARY

(a.) The findings of Blix and Ohlin (1) concerning a depressant action of pituitrin on the phosphatides of the blood are confirmed (by use of determination of the blood lipid phosphorus), although in a quantitatively considerably smaller degree.

(b.) In sympathectomized dogs somewhat irregular results suggest that this effect is weakened if not entirely absent.

(c.) The effects of pitressin and pitocin are irregular. Yet, they suggest that both of these fractions of pituitrin exert a certain influence on the blood lipid phosphorus similar to that of pituitrin.

(d.) There cannot be produced a marked increase of the blood lipid phosphorus by intravenous injection of egg yolk.

I wish to express my gratitude to Professor Cannon for the permission to use his sympathectomized animals and for all facilities granted to me in his laboratory.

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# STUDIES IN THE PHYSIOLOGICAL PROPERTIES OF THE GROWTH-PROMOTING EXTRACTS OF THE ANTERIOR HYPOPHYSIS\*

HAROLD M. TEEL AND HARVEY CUSHING

From the Laboratory of Surgical Research, Harvard Medical School  
BOSTON

Evans and Long (1), in 1921, first reported remarkable overgrowth in female rats, which had been brought about by daily intraperitoneal injections of a saline emulsion of the fresh bovine anterior hypophysis. They also called attention to a peculiar effect which these emulsions had on the oestrous cycles and the ovaries of the injected animals. Oestrus occurred infrequently or was completely inhibited, and the ovaries, in many instances, were found to be enlarged. The enlargement proved to be due to the proliferation of lutein tissue in the walls of follicles, which was frequently so extensive that solid corpora lutea were formed. Ova were found enclosed within many of these corpora showing that their formation had not been preceded by true ovulation as occurs in the formation of normal corpora lutea. In young animals the onset of the first oestrus was delayed.

Further work by Evans (2) and his associates led to more efficient methods of extracting the growth-promoting principle from the gland.

Four years ago studies were begun in this laboratory on the properties and effects of these growth-stimulating extracts. Preliminary studies with extracts prepared according to the methods of Evans and his associates fully confirmed their observations on rats, a veritable gigantism resulting after several months' injection.

However, the procedure of the California workers, of preparing the extracts daily from fresh glands, proved so time-consuming and expensive that we cast about for a method of preparing sterile extracts which could be preserved. By means of a slight modification of the method of Evans, and the use of the Seitz filter, it became possible to prepare a sterile limpid extract which retained its activity for weeks if kept at freezing temperature (3).

With this readily absorbable fluid experiments previously restricted to rats were extended to dogs, a step which seemed advisable for several reasons. In the first place rats retain the ability to grow throughout life. Moreover, their bony epiphyses never completely close so that a syndrome simulating acromegaly could hardly be expected in this species. On the other hand, in the dog, in which the epiphyses do close, the production of a state resembling acromegaly in man seemed possible. Furthermore, it was highly desirable to extend the studies to canines because the use of this

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larger animal permits chemical and metabolic studies on blood and urine that are difficult or impossible in the rat.

Injections, continued for over a year in a pure-bred English bulldog (with littermate control), brought about a condition closely simulating human acromegaly (4). The experimental animal grew rapidly and developed marked aeral enlargement. Many of the symptoms and signs of clinical acromegaly became apparent, including a voracious appetite, asthenia, hypotonia, sialorrhea and spontaneous lactation, as well as disproportionate enlargement of the tongue, and considerable increase in the amount, and change in the texture, of the cutaneous tissues. The injected animal never showed evidence of oestrus.

Definite skeletal overgrowth was demonstrable at postmortem (Fig. 1), and what was of even greater interest, a remarkable splanchnomegaly comparable to that characterizing human acromegaly (5) was found. The whole digestive system, especially the liver, was greatly hypertrophied as

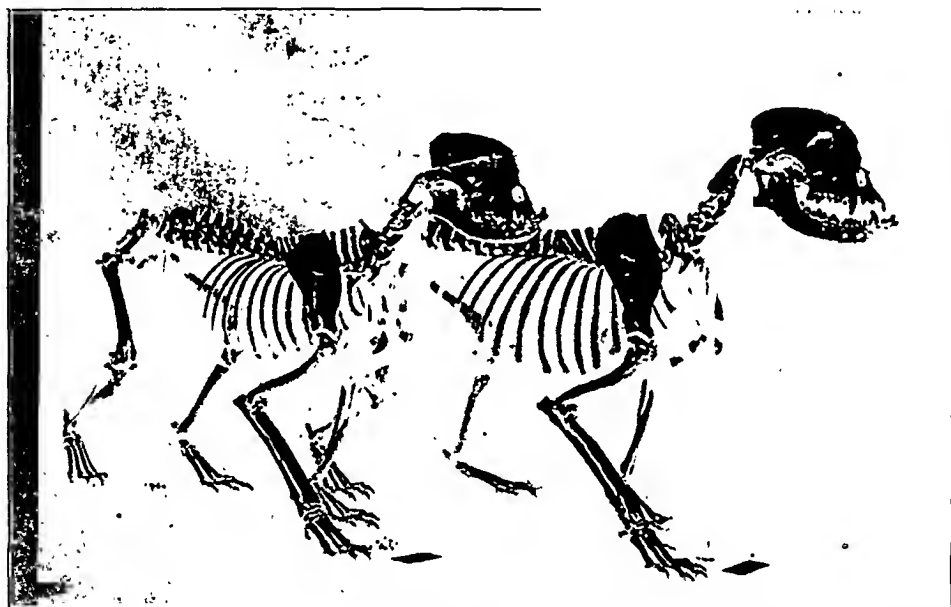


Fig. 1.—Skeleton of thorough-bred female English bulldog after 14 months of daily injection with hypophyseal growth-promoting extract. The skull of the littermate control is shown on the left for comparison.

were the thyroids, adrenals, heart, and kidneys, but the disproportion in size was greatest in the genital tract. The vagina and uterus had become greatly hypertrophied and the ovaries were four times the weight of those of the control, the increase in size of the latter organs being largely due to increase in stroma. A few large follicles and many atretic ones were seen but there were no corpora lutea.

It was perhaps unfortunate and misleading that the first prolonged experiment was made on a bulldog, an animal that might be regarded as potentially having acromegalic features. Entirely comparable and equally definite experimental overgrowth has since been produced in other animals



Fig. 2.—This mongrel male Alredale was approximately 14 months old and had not gained in weight during the six weeks of observation before injections were begun. Photograph taken after six months of daily injections when the animal had doubled in weight and marked acral enlargement was apparent. Autopsy revealed striking splanchnomegaly.



Fig. 3.—Year-old littermate Boston terriers of pedigreed stock. At the age of five months, when injections were begun, the experimental animal (right) was slightly smaller than the control.

both male and female of other breeds (Fig. 2 and 3). In males there results a loss of libido associated with a varying amount of atrophy in the testes which is sometimes extreme.\*

Having obtained these pronounced effects on the growth and behavior of the animals, we proceeded to study their food and water metabolism.

#### STUDIES IN BLOOD CHEMISTRY

In collaboration with Dr. O. Watkins of the Department of Biochemistry (6), certain of the constituents of the blood of fasting dogs were followed after parenteral administration of the growth-promoting extracts. It was found that about twenty hours after the last feeding the non-protein nitrogen in the blood of the normal animal reaches a fasting level at which it remains practically constant. After this level is once established there

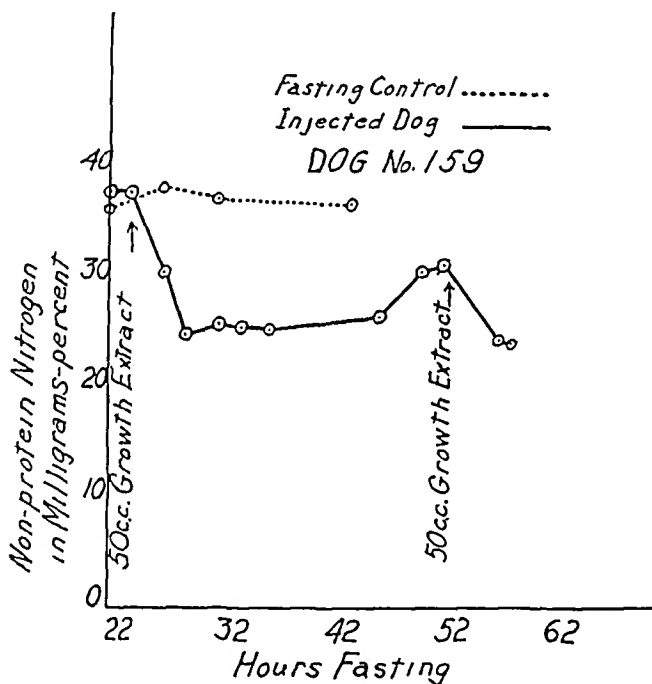


Fig. 4.—Graph showing the effect of intraperitoneal injection of growth-promoting extract upon the level of non-protein-nitrogen in the blood of a fasting dog. (The relatively constant value in a representative control experiment is shown in the dotted line for comparison.) In this experiment the injection was repeated when the non-protein-nitrogen had begun to rise again to the normal fasting level, resulting in a repetition of the effect.

is no further lowering; indeed, after prolonged fasting (weeks) the non-protein nitrogen tends to rise slightly as shown by Morgulis. Accordingly the experiments were all begun after at least twenty hours' fast and it was found that injection of the growth extracts led to a further considerable drop in the level of the fasting non-protein nitrogen, of from 20 to 30 per cent. This drop did not come immediately but only after a latent period of from three to six hours, after which the level remained low for some hours and did not rise again to the previous fasting level until the lapse of eighteen to twenty-four or more hours (Fig. 4). The fall in the non-protein

\*The effects of these relatively crude growth-promoting extracts on the gonads and genital system should not be confused with the more recently described *gonad stimulating* effects of other preparations from the anterior lobe.

nitrogen was distributed among urea, amino acid, and "undetermined" nitrogen, roughly in proportion to their respective normal concentrations in normal fasting blood.

Control injections of extracts after boiling, which is known to destroy the growth principle, brought about no such response (Fig. 5). Posterior lobe extracts were also ineffective in this respect as was ox serum which had been diluted with a sodium acetate solution to the point at which the protein and sodium acetate concentrations corresponded with those in the growth extracts.

Slight changes in serum calcium and inorganic phosphorous were also observed but were not constant and they were not followed in a large

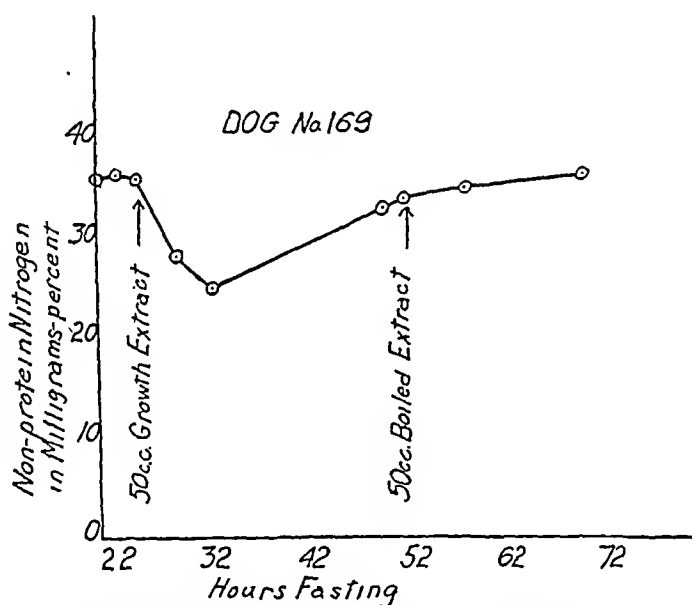


Fig. 5.—Graph showing, first, the effect of an active growth-promoting extract upon the level of non-protein-nitrogen in the fasting blood; and second, the inactivity of the same preparation after boiling. (Compare this with figure 4 in which the active preparation was repeated.)

enough series of cases for us to be certain of any real effect. There were no significant fluctuations in the blood sugar during the period of the experiments.

The disappearance of nitrogen from the blood following injection suggested that it was either excreted in the urine or was stored in the tissues. The latter supposition appeared to be supported by the rapid gain in weight of the injected animals, and especially by the splanchnomegaly which follows such treatment.

A few analyses of two hour samples of urine taken before and after injection convinced us that the two-hour excretion of nitrogen in the urine fluctuated too greatly to give reliable information on this score.



## STUDIES ON THE METABOLISM OF NITROGEN PHOSPHORUS AND CALCIUM

Failure to prove the fate of the disappearing non-protein nitrogen from the blood by analysis of urine for brief periods preceding and following injection led to more prolonged balance-experiments.

In collaboration with Dr. Walter Bauer of the Massachusetts General Hospital the following observations were made. The dogs were fed a constant amount of a modification of Cowgill's synthetic diet and the elimination of nitrogen calcium and phosphorus was determined for a period preceding and another during injections of the growth-stimulating extracts. In spite of the fact that the diet, and hence the calorific intake, remained constant, analyses of urine showed that there was marked retention of nitrogen; moreover phosphorus practically disappeared from the urine. The calcium excretion in the urine on the other hand was considerably increased during the first few days following injection.

## STUDIES IN GASEOUS METABOLISM

Having found that a notable retention of nitrogen follows injections of the growth-promoting substance in spite of the fact that the calorific intake remains constant, it seemed not unlikely that if this observation were correct the gaseous metabolism might compensatorily be diminished.

Preliminary determinations of the basal metabolic rate of the injected dogs showed that the rate at least was not accelerated, the figures actually indicating a diminished rate. Since Dr. Benedict's most recent and highly accurate metabolism-apparatus for rats was available in the laboratory of Dr. Hoskins and Dr. Lee, with Dr. Lee's (7) cooperation, the metabolism of four of our giant-rats was determined. In each animal the basal metabolic rate was definitely diminished, the average of the determinations for all four of the animals being 13 per cent below that of a large control series of other normal rats. In two of the giant animals the injections were omitted for three weeks during which time the animals lost some weight although they were still considerably heavier than their controls. Metabolism determinations on these animals after discontinuance of the injections showed that the rates had risen to within normal limits.

It would appear that the drop in the level of the blood non-protein nitrogen, the retention of nitrogen from the diet, and the diminished metabolic rate following injection are not incompatible findings.

## STUDIES IN WATER METABOLISM

During the course of prolonged experiments on growth, it was casually observed that there was considerable diuresis following injection of some preparations of the growth-promoting extracts.

Measurement of the water intake, urine output, and specific gravity for some days before, and following injections of the extracts, showed that some

of them possessed remarkable diuretic properties (Fig. 6). A single daily injection of 25 cc. in a number of instances increased the twenty-four hour intake and output more than ten fold. One animal whose average twenty-four hour output during the control period was 700 cc., after injections were begun, excreted as much as 7300 cc. of urine in twenty-four hours and the daily elimination remained above five liters during a week period of observation. The specific gravity of the twenty-four hour specimens fell from *circa* 1040 to *circa* 1003. Moreover, the diuresis did not begin for twenty-four or more hours following the first injection and the effect per-

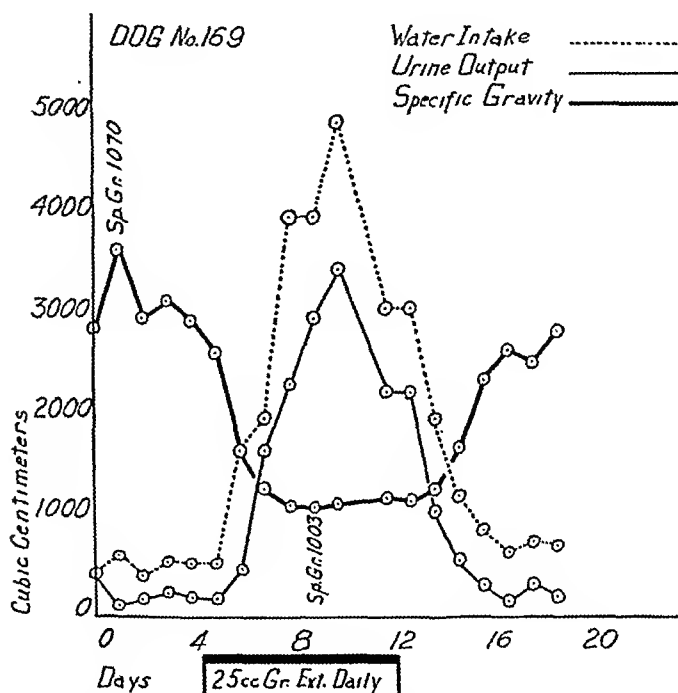


Fig. 6.—Graph showing the marked diuretic effect of a single daily injection of 25 cc. of growth-promoting extract. Not all the extracts which accelerated growth produced the diuretic effect.

sisted for two or three days following the last one. Not all of the growth extracts possess this diuretic effect, although there have been no extracts which produce diuresis which do not also stimulate growth in rats. We are not yet able to state whether growth and diuresis are due to the same substance.\*

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\*Recently Dr. Oliver Kamm of Parke, Davis and Company has informed us that he has repeated the experiments on diuresis. He states that he has evidence which suggests that the diuresis may be due to a non-specific protein reaction, rather than a specific hypophyseal effect.

# DOES THE ZONDEK PITUITARY HORMONE INFLUENCE THE GROWTH OF THE BODY?

P. V. BOTCHKAREFF and A. P. PREOBRAJENSKY  
From the State Institute of Experimental Endocrinology  
Director: Prof. Dr. G. P. Sakharoff  
MOSCOW

It is beyond the least doubt that the anterior lobe of the pituitary body is the source of a hormone stimulating the growth both of the whole body and of various separate organs. Not only do the clinical observations upon dwarfism, gigantism and acromegaly support this proposition, but also the experimental studies, particularly the cessation of the growth and development of the body following ablation of the anterior lobe of the hypophysis.

For the most part attempts to provoke gigantism in animals by means of pituitary extracts have given but doubtful results. It is true, however, that Wulzen's experiments on planarian worms (1), Uhlenhuth's on axolotls (2), Long and Evans' on rats (3) and Putnam's on dogs (4) have shown the possibility of stimulating the growth of the young animals by the aid of parenteral injections of anterior pituitary substance or of its extracts. These extracts, however, were of too indefinite composition, and no opinion could be formed as to the nature and properties of their active principles.

After Zondek's discovery of the anterior pituitary hormone provoking the rapid growth and development of the sexual glands both in females and in males, many investigators, including one of us (5), showed that using the method pointed out by Zondek it is easy to obtain from the pituitary body and from the urine of the pregnant women a substance which is the "primary sexual hormone," and is capable of provoking in a very short time the full development of the sexual glands in infantile animals. We did not find, however, either in literature or in our own experiments any evidence concerning the increase of the growth of these animals. We supposed then that it was the insufficient quantity of the hormone, as well as the short duration of the experiment, that were the causes of the absence of such an effect. For this reason we have performed a series of experiments on the white rats, using large quantities of this hormone and prolonging the experiment to 50 days.

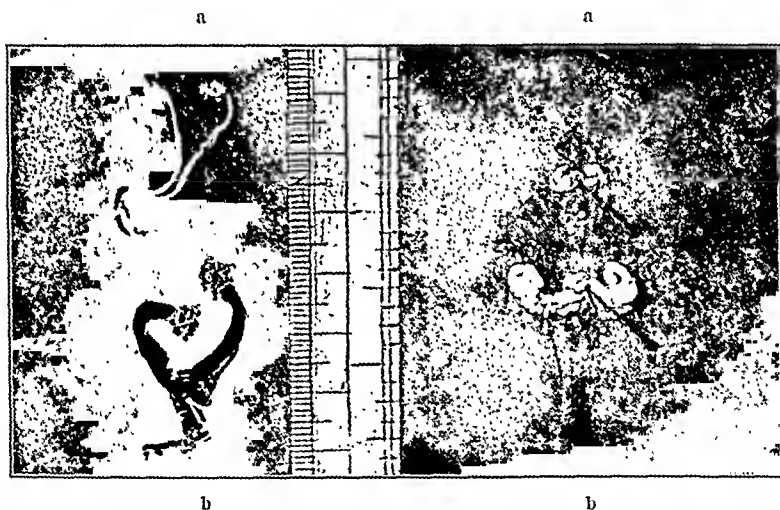
As a preparation of anterior pituitary hormone, we used the "Pitnerin A" of the State Institute of Experimental Endocrinology in Moscow; this preparation contained 20 mouse units per cubic centimeter. The experiment was performed on 24 rats. It is impossible to have such a quantity of animals belonging to one litter; so we had chosen our rats that every two or three rats and the control animal of the same sex be-

longed to the one litter (see table). All animals were kept under similar conditions of environment and nutrition. Each rat received daily 0.5 c.c. of the above mentioned preparation, i.e., 10 mouse units. The control animals received an equal quantity of physiological saline solution. The weighing was performed weekly and we started studying the vaginal secretion in females as soon as that became possible.

The experiment of 50 days' duration has given the following results:

(1) In all females which received the hormone the phenomena of the oestrous cycle appeared on the 4th to 7th day from the beginning of the experiment. None of the control females showed them during the first month.

(2) After two weeks some animals were killed and dissected. In the females which had received the hormone, uteri and ovaries were enormously increased, the average weight of the uterus being 0.45 gm., as compared with 0.065 gm. in control animals. The corresponding weight of the ovaries was 0.075 and 0.03 gm. In males it was possible to note a



Photographs of uterus and ovaries and of seminal vesicles, respectively, of control animals (above) and of injected animals (below).

considerable growth of seminal vesicles (average weight of them was 0.19 gm., while in the control males it was 0.04 gm.), while the testicles presented less difference in weight, the latter being correspondingly of 0.81 and 0.77 gm.

The accompanying photograph shows the difference in size of those organs in normal animals (a) and in animals which received the hormone (b).

(3) Notwithstanding so intense an action of the hormone on the sexual system, no difference was observed between the growth of the animals used in the experiment and of the control animals. The following table presents the corresponding numerical data:

## I. FIRST SERIES

Group	Animal	Litter	Weight in Grams						
			25.IX	3.X	10.X	17.X	24.X	31.X	14.X
Females.....	1	1	51.0	64.5	83.5	97.0	109.5	117.0	139.0
	2	1	51.0	61.5	73.5	81.0	81.5	93.0	120.0
	3	2	43.0	62.0	81.5	100.5	109.0	115.0	122.0
	4	2	40.0	58.0	75.0	87.5	101.5	115.0	146.0
Average.....			46.3	61.5	78.4	91.5	100.4	110.0	131.8
Control Females....	5	1	50.0	63.0	81.0	91.5	101.0	108.0	129.0
	6	1	50.0	70.5	82.5	94.0	101.5	109.0	128.0
	7	2	38.0	57.5	76.5	91.0	96.0	111.0	148.0
			46.0	63.7	80.0	92.2	99.5	109.3	135.0
Males.....	8	1	50.0	70.0	90.5	98.0	118.5	137.0	172.0
	9	2	42.0	62.5	90.0	104.0	121.5	142.0	184.0
			46.0	66.3	90.3	101.0	120.0	139.5	178.0
Control Males.....	10	1	52.5	70.5	95.0	101.0	126.5	149.0	184.0
	11	2	46.0	62.5	87.0	89.5	116.0	137.0	176.0
	12	2	43.0	63.5	85.0	90.0	108.5	150.0	174.0
			47.2	65.5	89.0	93.5	110.0	145.3	178.0

## II. SECOND SERIES

Group	Animal	Litter	Weight in Grams					
			4.X	11.X	18.X	25.X	3.XI	14.XI
Females . . . . .	13	3	40.0	56.0	81.5	89.5	115.0	133.0
	14	3	38.0	57.5	75.5	Killed		
	15	3	36.0	57.5	85.5	91.0	125.0	153.0
	16	4	33.0	49.5	67.5	Killed		
	17	4	34.0	55.5	74.0	83.5	105.0	122.0
Average . . . . .			36.2	55.2	76.9	88.0	115.0	136.5
Control Females . . . . .	18	3	38.5	56.5	71.5	Killed		
	19	4	38.0	55.0	75.0	85.0	116.0	136.0
			38.3	55.8	73.3	85.0	116.0	136.0
Males.....	20	3	40.0	62.5	88.5	97.5	131.0	181.0
	21	4	37.5	54.0	71.5	Killed		
	22	4	39.0	58.5	83.5	Killed		
			38.8	58.3	81.2	97.5	131.0	181.0
Control Males.....	23	3	38.0	59.0	89.0	100.5	140.0	184.0
	24	4	36.0	53.5	78.5	Killed		
			37.0	56.3	83.8	100.5	140.0	184.0

Graphically these relations are shown in Charts 1 and 2.

## SUMMARY

In 14 young rats injections were made of Zondek's anterior lobe pituitary hormone. The control animals were injected with saline solu-

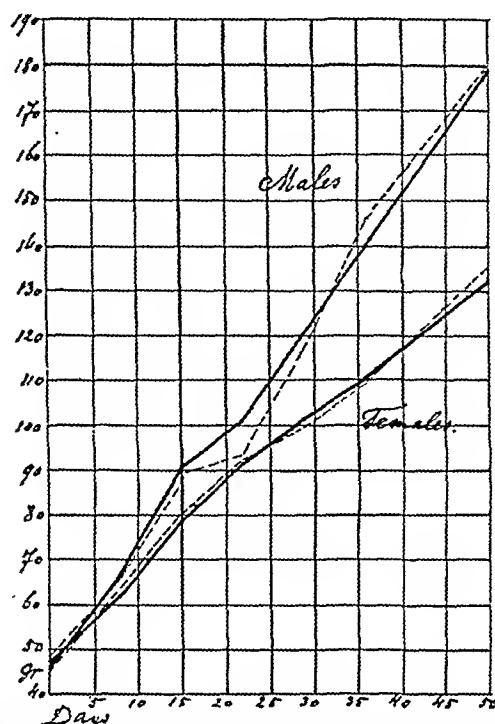


Fig. 1. Growth of control and of injected rats, series I.

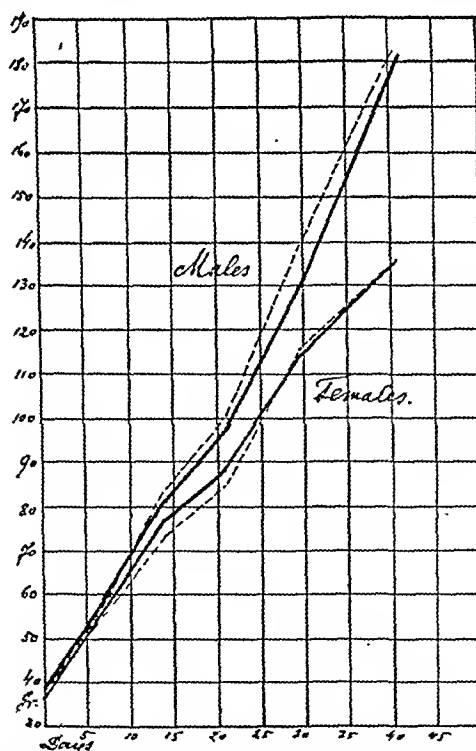


Fig. 2. Growth of control and of injected rats, series II.

tion. Although marked stimulation of the growth of the sex organs occurred, there was no influence on the growth of the young animals. It is probable that the growth-stimulating action of the pituitary body is due to another not yet isolated hormone of this organ.

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# THE EFFECT OF INTRAPERITONEAL INJECTION OF POTASSIUM IODIDE ON THE PROLIFERATIVE ACTIVITY OF THE THYROID GLAND IN RATS

K. S. CHOUKE, M.A., M.D.

From the Department of Pathology, Washington University  
ST. LOUIS

and the Department of Anatomy, University of Colorado  
DENVER

Loeb (1) has shown that oral or intraperitoneal administration of potassium iodide to guinea pigs does not prevent the compensatory hypertrophy which occurs after extirpation of the greater part of the thyroid gland. Gray and Loeb (9), Rabinovitch (2), McCordock (7), and Silberberg (3) have subsequently observed that the administration of potassium iodide orally or by intraperitoneal injections to normal guinea pigs for a certain length of time results in a very pronounced increase in the mitotic proliferation of the thyroid epithelium. It also leads to a slight increase in the size of the epithelium, to a slight softening of the colloid and to a marked increase in the number of phagocytes within the colloid. Marine (4) on the other hand maintains that the intraperitoneal injection of KI to guinea pigs previously subjected to partial thyroidectomy always prevents the onset of compensatory hypertrophy. Des Lign  ris (5) had previously found that feeding KI in dogs causes an increase in the amount and hardness of colloid.

Administration of KI in Graves' disease during a short period of time causes, in many cases, an increase in the amount of colloid and a flattening of the epithelium, which may, perhaps, be the result of pressure exerted by the colloid. On the other hand, KI can also exert a stimulating effect on the thyroid gland in man; it can transform a resting colloid goiter into toxic goiter or into a condition corresponding to Graves' disease.

The experiments referred to above, in which a stimulating effect of KI was observed, were carried out in guinea pigs. It was of interest to study the effect of potassium iodide in another species with the same methods which had been used in the case of the guinea pig. We selected for this purpose the white rat. In previous experiments Loeb and Bassett (8) have already observed that extracts of anterior pituitary glands of cattle which are very active when administered to guinea pigs, are much less active in the rat. These experiments indicated that in the latter species the thyroid gland may be less responsive to stimulating agencies than it is in the guinea pig.

In this investigation three sets of rats weighing between 100 and 155 grams, were used. The rats of the first set received intraperitoneal injections daily of 0.005 gm. of potassium iodide dissolved in 0.5 cc. of sterile distilled water; the animals of the second set were injected with



0.025 gm. daily. The third set serving as controls, did not receive any injections of potassium iodide. The injections were given to different groups of animals daily for periods of 10, 15, 20, or 30 days respectively; at the end of each of these periods the thyroids were removed and studied according to the method used by Loeb, Gray and Rabinovitch (6).

#### COUNTS OF MITOSES

*Control Animals:* The number of mitoses found in the control animals varied between 0 and 1538, the average being 208 (Table I). If we discard rat 34, having an unusually high count of 1538 mitoses, the average number of mitoses per gland would be 106. By discarding rat 1 showing no mitoses at all and rat 34 with 1538 mitoses, the average falls to 114.

TABLE I  
CONTROL RATS

Rat No.	*No. Mitoses per Gland	Sex	Original Weight in gms.	Final Weight in gms.	Loss or Gain Weight gms.
1	0	F	—	85	—
6	20	F	—	140	—
7	38	F	125	135	+10
10	40	M	130	155	+25
11	60	F	140	165	+25
18	219	F	130	135	+ 5
19	60	M	115	125	+10
26	156	M	120	115	— 5
27	342	M	100	120	+20
34	1538	M	—	—	—
35	80	M	—	—	—
36	100	M	—	—	—
37	139	M	—	—	—
38	120	M	—	—	—
Average	114	—	123	131	+ 8

\*Both lobes, excluding the isthmus.

*Animals Receiving Intraperitoneal Injections of KI for Ten Days:* Animals that were given intraperitoneal injections of KI for a period of ten days neither showed a noticeable increase nor a decrease in the number of mitoses. There was no marked difference in the animals receiving the larger dose (0.025 gm.), and the ones receiving the smaller dose (0.005 gm.); the average count in the former being 140 and in the latter 119 mitoses.

*Animals Injected with KI for Fifteen Days:* This group does not show any striking variations either from the controls or from the ten-day group. The average number of mitoses in this group, for the animals receiving small doses of KI was 193, and for those receiving large doses it was 110. The apparent difference between these two groups is not very great and can be considered within the limits of experimental variation.

*Animals Injected with KI for Twenty Days:* In this group the average number of mitoses for all animals was 128; for the rats receiving the small dose the average was 53, and for those receiving the large dose it was 204. Again there is no appreciable variation in the number of mitoses from the controls.

*Animals Injected with KI for Thirty Days:* The average number of mitoses in this group for the animals injected with the small dose was 168 and for those receiving the large dose was 123. No striking deviation from the controls or from the other groups is seen.

It can therefore be stated that in the rat the intraperitoneal injection of KI does not have any marked effect on the proliferative activity of the thyroid gland, as judged from the number of mitoses found in this organ. It causes neither a decrease nor an increase. The number of mitoses found in each animal receiving intraperitoneal injections of KI is shown in Table II.

TABLE II  
RATS RECEIVING INTRAPERITONEAL INJECTIONS OF KI

Rat No.	*No. of Mitoses per Gland	Sex	Original Weight in gms.	Final Weight in gms.	Loss or Gain in Weight gms.	†Small or Large Dose	No. of Days Injected
2	0	M	125	130	+ 5	L	10
3	38	F	155	150	- 5	L	10
8	383	F	145	135	-10	L	10
4	154	M	130	150	+20	S	10
5	40	M	130	130	0	S	10
9	162	F	145	140	- 5	S	10
12	338	M	125	135	+10	S	15
14	181	M	125	130	+ 5	S	15
15	60	M	130	150	+20	S	15
13	150	M	115	110	- 5	L	15
16	101	F	135	135	0	L	15
17	78	F	125	105	-20	L	15
21	79	M	110	125	+15	S	20
22	40	M	110	115	+ 5	S	20
25	40	M	120	125	+ 5	S	20
20	453	M	115	130	+15	L	20
23	20	M	110	100	-10	L	20
24	140	F	110	145	+35	L	20
29	220	M	115	110	- 5	S	30
31	109	M	105	110	+ 5	S	30
33	176	M	110	135	+25	S	30
28	140	M	130	125	- 5	L	30
30	210	M	115	110	- 5	L	30
32	20	M	125	130	+ 5	L	30
Average	139	—	123	127	+ 4	—	—

\*Both lobes, excluding the isthmus.

†Small dose = 0.005 gm. Large dose = 0.025 gm.

## STRUCTURAL CHANGES IN ACINI, EPITHELIUM AND COLLOID

In the control animals the acini are regular and usually small to medium in size, although occasionally they may be somewhat larger. They are lined with cuboidal epithelium and filled with solid, intensely staining, slightly retracted colloid. Sometimes vacuoles are present in the peripheral parts of the colloid. The number of phagocytes in the colloid in the lumen of the acini is variable. In some acini no phagocytes are seen, in others one may see a few phagocytes. The histological character of the thyroid in rats injected with potassium iodide does not differ materially from that seen in the controls. The size of the alveoli is approximately the same in the two groups. The epithelium in general is cuboidal but in places it may show a tendency towards a columnar shape. The colloid does not differ to any appreciable degree from that found in the controls, although occasionally it may show signs of softening processes in the glands of the animals receiving KI. The number of phagocytes does not differ noticeably in the two groups. In this connection it may be stated that on the whole the acinar epithelium of the thyroid in the rat is somewhat higher than in the guinea pig.

There are thus no decided differences in the microscopic appearance of the thyroid glands of the rats injected with KI and of the controls. But in individual cases considerable variations are present. In some animals the colloid may be of medium consistency while in others it may be hard. The average height of the acinus cells shows some variations, but in this respect also there is no consistent difference between the two groups.

The microscopic structure of the rat thyroid is somewhat different from that of the guinea pig. The three zones of different sized acini as described by Loeb and McCordock in the guinea pig thyroid are not present in case of the rat. In the latter animal the acini are usually somewhat larger in the periphery than in the center. The colloid is also more often retracted from the walls of the peripheral acini than from the central ones.

Control rat No. 34 needs especial mention for the reason that the thyroid gland of this animal showed 1538 mitoses, which is an exceptionally large number. Most of these mitoses were in the prophase or metaphase stage. No explanation for this unusually high proliferative activity seems to be available.

## DISCUSSION

In contrast to the definite and large increase in the proliferative activity of the thyroid gland which takes place in guinea pigs receiving potassium iodide orally or intraperitoneally, we find no marked change in the number of mitoses in the thyroid gland of rats as a result of intraperitoneal injections of KI. There is no noticeable difference in the number of mitoses in the thyroid gland of the rats receiving KI injections for 10, 15, 20, or 30 days and in the controls. Neither do variations in the dose of KI given seem to cause here any change in the proliferative activity of the thyroid gland. The average weight of these animals was 0.125 kgm.

The doses of KI given were 0.005 gm. and 0.025 gm. in the two groups respectively. In other words, these rats received each day 0.04 gm. and 0.2 gm. KI dose per kilogram of body weight, which is equivalent to 2.8 gm. and 14.0 grams respectively per kilogram of body weight in an average man weighing 70 kgs. Even the smaller of these doses is somewhat larger than the usual dose of this drug given in man, while the larger dose would be excessive in case of man. If KI had any effect on the mitotic activity of thyroid gland in the rat it would have become noticeable with these doses. We may then conclude that in the rat potassium iodide has apparently no effect on the proliferative activity of the thyroid gland. The average number of mitoses in the rat generally is smaller than in the guinea pig. This may be due to the smaller size of the thyroid gland of this animal; but, as stated above, there are indications that the thyroid gland in the rat is more inert to various stimuli than the thyroid gland in the guinea pig. Thus Loeb and Bassett found that while extracts of anterior pituitary substance cause a very pronounced hypertrophy and hyperplasia in the thyroid gland of the guinea pig they have very little effect on the structure of the rat thyroid.

The gain or loss in body weight in the individual rats during the course of these experiments does not correspond to the increase or decrease in the number of mitoses in the thyroid gland, neither does the sex of the animals seem to be a factor in the increase or decrease of the mitotic activity of this organ.

#### SUMMARY AND CONCLUSION

The intraperitoneal injection in daily doses of 0.005 gm. and 0.025 gm. of KI in rats for periods of 10, 15, 20, and 30 days does not cause any appreciable change in the proliferative activity of the thyroid gland, neither does it produce any noticeable change in the structure or character of the colloid of this organ.

The average number of mitoses in the normal thyroid gland of rats is slightly lower than in guinea pigs.

The effect of administration of KI in the rat is therefore different from that observed in the guinea pig. There is some indication that, in general, the thyroid gland of the rat is less responsive than the thyroid gland of the guinea pig to various kinds of stimulation.

The author is indebted to Professor Leo Loeb of Washington University, St. Louis, for advice and assistance during this study at the Marine Biological Laboratory, Woods Hole, Massachusetts.

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# THE RESULTS OF ORAL ADMINISTRATION OF AMNIOTIN TO MONKEYS\*

J. A. MORRELL, H. H. POWERS, J. R. VARLEY AND J. DE FRATES

From the Research and Biological Laboratories of E. R. Squibb & Sons  
NEW BRUNSWICK, N. J.

In previous experimental work we showed that when amniotin is administered by the vaginal route 2.5 times as much was necessary as when injected subcutaneously to produce an artificial sex cycle. This ratio was found to be the same in spayed rats and in ovariectomized monkeys.

Until the present time no satisfactory evidence has been given to show whether or not the follicular hormone is active when given by mouth. Many have thought that the hormone was destroyed by the digestive enzymes. Hannan claims that he obtained an estrus reaction in spayed rats when he administered 100 times the ordinary dosage.

We administered amniotin by stomach tube to the ovariectomized monkeys (*Macacus rhesus*) in our colony. After some preliminary difficulty in getting the stomach tube inserted no trouble was experienced. The amniotin was administered once a day for five consecutive days. All monkeys used had been under observation for months. All were completely ovariectomized. The ordinary commercial preparation of amniotin and special solutions of the hormone in alcohol and glycerin were used. No difference was noted in either the types of reaction nor the amounts necessary. Vaginal spreads were taken daily and observations made of the condition of the sexual skin.

In a preliminary group of 20 monkeys, dosages varying from 700 Allen-Doisy units up to 4200 Allen-Doisy units were administered by stomach tube. These were special alcohol glycerin solutions of amniotin. In all cases menstruation was established.

TABLE I

Amniotin Used—P 520—Experimental material—Oily substance dissolved in 50% glycerin and 50% alcohol.

Five doses were given, 1 daily for 5 consecutive days by stomach tube.

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Feeding and Menses, Days
1	2/10/30 to 2/14/30	700	11	5	14
5	2/10/30 to 2/14/30	700	9	4	16
7	2/10/30 to 2/14/30	700	11	7	15
12	2/10/30 to 2/14/30	700	15	9	22
19	2/10/30 to 2/14/30	700	9	2	18
21	2/10/30 to 2/12/30	840	7	4	15
23	2/10/30 to 2/14/30	1400	9	3	14
24	2/10/30 to 2/14/30	1400	8	6	14

\*Read before The Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

TABLE I—Continued

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Feeding and Menses, Days
27	2/10/30 to 2/14/30	1400	7	5	12
28	2/10/30 to 2/14/30	1400	9	6	14
30	2/10/30 to 2/14/30	2800	6	9	10
31	2/10/30 to 2/14/30	2800	6	3	14
33	2/10/30 to 2/14/30	2800	11	6	18
34	2/10/30 to 2/14/30	2800	15	7	19
35	2/10/30 to 2/14/30	2800	11	7	17
36	2/10/30 to 2/14/30	4200	9	5	14
37	2/10/30 to 2/14/30	4200	11	5	15
38	2/10/30 to 2/14/30	4200	8	5	15
39	2/10/30 to 2/14/30	4200	13	7	18
40	2/10/30 to 2/14/30	4200	8	5	14

Average Duration of Menses—5.5 Days.

Average Duration of Epithelial Growth—9.6 Days.

Average Number of Days between 1st injection and appearance of menstruation—15.4 Days. The longest flow lasted 9 days—the shortest 2 days. There was no correlation between the dosage given and the duration of the menstruation. Similarly there was no difference in the length of time between the administration of the amniotin and the onset of bleeding. It is worth noting that such massive doses as 4200 Allen-Doisy units to these small animals produced no toxic effects nor secondary reactions.

A second group of 15 monkeys were given orally, dosages varying from 100 to 800 Allen-Doisy units. The same preparation as above was used—a glycerin alcohol solution. Four animals on 100 units and three on 200 units did not respond. Four on 400 and four on 800 units gave a menstrual reaction. As in the previous group the duration of the menstrual flow showed no relation to the dosage. The average length of menstruation was 4.9 days.

TABLE II

Amniotin Used—P 520—Experimental material—Oily substance dissolved in 50% glycerin and 50% alcohol.

Five doses were given, 1 daily for 5 consecutive days by stomach tube.

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Feeding and Menses, Days
30	3/17/30 to 3/21/30	100	0	0	0
31	3/17/30 to 3/21/30	100	0	0	0
33	3/17/30 to 3/21/30	100	0	0	0
34	3/17/30 to 3/21/30	100	0	0	0
35	3/17/30 to 3/21/30	200	0	0	0
36	3/17/30 to 3/21/30	200	0	0	0
38	3/17/30 to 3/21/30	200	0	0	0
40	3/17/30 to 3/21/30	400	8	6	18
53	3/17/30 to 3/21/30	400	5	8	14
54	3/17/30 to 3/21/30	400	2	1	15
55	3/17/30 to 3/21/30	400	4	8	12
60	3/17/30 to 3/21/30	800	6	5	18
64	3/17/30 to 3/21/30	800	5	2	14
65	3/17/30 to 3/21/30	800	6	4	16
67	3/17/30 to 3/21/30	800	3	5	12

Average Duration of Menses—4.4 Days.

Average Duration of Epithelial Growth—4.9 Days.

Average Number of Days between 1st injection and appearance of menstruation—14.4 Days.

About 10 days after menstruation had ceased these monkeys were divided again into two groups. The ordinary commercial Amniotin was given to one group by injection and to the second group by stomach tube.

Thirteen monkeys were injected twice a day for 6 days. The total dosage varied from 25 to 150 Allen-Doisy units. One animal out of two menstruated on 75 units and the four on 100 and 150 units. In no case was menstruation obtained with less than 75 units.

TABLE III

Amniotin Used—P 568—Commercial Stock Preparation.

Two injections daily for 6 consecutive days.

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Injection and Menses, Days
2	4/21/30 to 4/26/30	25	3	0	0
5	4/21/30 to 4/26/30	25	2	0	0
7	4/21/30 to 4/26/30	40	6	0	0
12	4/21/30 to 4/26/30	40	6	0	0
19	4/21/30 to 4/26/30	50	6	0	0
21	4/21/30 to 4/26/30	50	6	0	0
27	4/21/30 to 4/26/30	50	5	0	0
30	4/21/30 to 4/26/30	75	1	0	0
31	4/21/30 to 4/26/30	75	13	2	0
33	4/21/30 to 4/26/30	100	8	4	18
34	4/21/30 to 4/26/30	100	7	2	25
35	4/21/30 to 4/26/30	150	8	2	21
36	4/21/30 to 4/26/30	150	10	3	15

Sixteen monkeys were given the same stock solution by stomach tube. This was given once a day for five days. The dosages varied from 100-500 Allen Doisy units. None of the eleven animals on 100, 150, 200 or 300 units menstruated. Of the remaining five all gave a menstrual reaction.

TABLE IV

Amniotin Used—P 568—Commercial Stock Preparation.

Given by stomach tube once daily for 5 consecutive days.

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Feeding and Menses, Days
38	4/21/30 to 4/25/30	100	2	0	0
40	4/21/30 to 4/25/30	100	1	0	0
53	4/21/30 to 4/25/30	150	0	0	0
60	4/21/30 to 4/25/30	150	0	0	0
64	4/21/30 to 4/25/30	150	2	0	0
7	2/10/30 to 4/25/30	200	0	0	0
12	2/10/30 to 4/25/30	200	0	0	0
19	2/10/30 to 4/25/30	200	2	0	0
21	2/10/30 to 4/25/30	300	2	0	0
23	2/10/30 to 4/25/30	300	2	0	0
24	2/10/30 to 4/25/30	300	2	0	0
	4/25/30	400	4	2	22
	4/25/30	400	3	2	16
	4/25/30	400	4	2	15
	4/25/30	500	6	7	10
	4/25/30	500	5	3	22

\*Read before The Assoc June 23, 1930.

This was again checked by taking another commercial lot of amniotin. Two groups were given this by injection and by stomach tube.

In the 10 monkeys injected, 3 at 68 units and 3 at 90 units, gave a menstrual reaction. The remainder at 30 and 45 units failed to respond.

TABLE V

Amniotin Used—P 607—Commercial Stock Preparation.  
Injections twice daily for six consecutive days.

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Injection and Menses, Days
36	5/24/30 to 5/29/30	30	5	0	0
34	5/24/30 to 5/29/30	30	7	0	0
31	5/24/30 to 5/29/30	45	5	0	0
30	5/24/30 to 5/29/30	45	6	0	0
27	5/24/30 to 5/29/30	68	7	3	17
21	5/24/30 to 5/29/30	68	7	3	16
19	5/24/30 to 5/29/30	68	5	3	17
7	5/24/30 to 5/29/30	90	5	6	17
5	5/24/30 to 5/29/30	90	7	4	16
2	5/24/30 to 5/29/30	90	9	4	16

Thirteen monkeys were given this preparation by stomach tube in dosages from 90 to 225 Allen-Doisy units. At 225, two out of four menstruated. Below that dosage only negative results were obtained.

TABLE VI

Amniotin Used—P 607—Commercial Stock Preparation.  
Fed once daily for 5 consecutive days by stomach tube.

Monkey No.	Dates of Feeding	Allen-Doisy Units	Duration of Epithelial Growth, Days	Duration of Menses, Days	Time Between Feeding and Menses, Days
38	5/24/30 to 5/29/30	225	5	0	0
40	5/24/30 to 5/29/30	225	5	3	18
60	5/24/30 to 5/29/30	225	4	0	0
64	5/24/30 to 5/29/30	225	7	3	17
65	5/24/30 to 5/29/30	180	0	0	0
67	5/24/30 to 5/29/30	180	0	0	0
68	5/24/30 to 5/29/30	180	0	0	0
69	5/24/30 to 5/29/30	135	0	0	0
70	5/24/30 to 5/29/30	135	0	0	0
71	5/24/30 to 5/29/30	135	0	0	0
73	5/24/30 to 5/29/30	90	0	0	0
75	5/24/30 to 5/29/30	90	0	0	0
76	5/24/30 to 5/29/30	90	0	0	0

## SUMMARY

A total of 64 monkeys were given Amniotin by stomach tube. In 33 of these when 400 or more units were given menstruation resulted. In 2 of 4 monkeys on 225 units bleeding occurred. The remaining 27 on lower dosages did not respond. There was no difference in the amount necessary whether the commercial preparation was used or a special glycerin alcohol solution.



A total of 23 monkeys were injected twice daily for 6 days. Eleven of these menstruated on dosages of 68 units or over. The remainder gave negative results.

Apparently then about 400 Allen-Doisy units are necessary when given by stomach tube to produce menstruation. About 75 units when injected will do the same thing. So the ratio between the oral and subcutaneous dosage is about 5:1.

In all our work with amniotin in monkeys, whether given by injection or by vaginal pessaries or by the oral route, it is apparent that a certain threshold amount must be administered to obtain the menstrual reaction. Any excess of that amount does not produce any greater effect nor any undesirable symptoms.

## Book Reviews

TESTICULAR GRAFTING FROM APE TO MAN. Serge Voronoff and George Alexandrescu. Translated by Theodore C. Merrill. Bretano's Ltd., London.

The scope of the book is sufficiently indicated by the title. Statistics are presented in 475 cases in which satisfactory postoperative reports were available. Results were considered successful if favorable effects persisted more than two years. In completely satisfactory operations the effects are stated to persist about six years. Among the various types of patients treated success is reported in from 22 to 91 per cent of the cases.

The book is well printed and the illustrations are clear.

LES SYNDROMES ENDOCRINES. R. Porak, 1929. G. Doin & Cie, Paris. Pp. 554. 2nd Edition.

The author has edited the second edition of this book in the same critical manner that characterized the first. He has evaluated the observations that have been made in Europe and in North and South America. His observations have been confirmed in the last four years as shown by publications in France and abroad. However, the endocrinologists are divided, the sceptics and the enthusiasts, the author belonging to the sceptical group. At the conclusion of his work the opinions of the enthusiasts are given and the reader has the two points of view presented for his consideration.

L'ENDOCRINOLOGIE ET LES ETATS ENDOCRINE-SYMPATHIQUES. II. A. C. Guillaume. 1929. G. Doin & Cie, Paris. Pp. 413.

With delightful clarity the author has set forth a great deal of material on the clinical aspects of endocrine disorders. The work represents, largely, however, an organization of much premature generalizing. Preciseness and clarity in this case are in their suggestion misleading because our knowledge of clinical endocrinology is neither precise nor clear. A false sense of security is also engendered by singling out for formal treatment under exact denomination a considerable number of the thousands of possible combinations of endocrine disorders. The formal bibliography includes some of the best and some of the worst monographs that have had wide currency. To the reader who can bring to bear an adequate critical judgment, the book can be commended as a source of much interesting information. It is marked as much, however, by omissions as by inclusions of important matter.

L'ENDOCRINOLOGIE ET LES ETATS ENDOCRINO-SYMPATHIQUES. III. LA CLINIQUE DES ENDOCRINES LES ETATS VISCERAUX. Guillaume, A. C., 1930. G. Doin & Cie., Paris. Pp. 597.

This third volume completes the work. It is devoted to the study of the endocrine-sympathetic system—sex, circulation, liver, nerve and mental disturbances. As in the two preceding volumes, this work differs from

similar works along this line in that the endocrines are not studied gland by gland but the disturbances are presented in the manner in which they appear in the clinic; that is to say, the thyroid, suprarenal, sex glands, etc., are not studied as such but as their disturbed functions appear in such diseases as rheumatism, menstrual disorders, cachexia, convulsions, circulatory trouble, etc.

ENDOCRINOLOGIA Y CRIMINALIDAD. M. Ruiz-Funes. 1929. Javier Morata, Madrid. Pp. 352.

Professor Ruiz-Funes of the University of Murcia has brought together and discussed philosophically a large mass of data from the world's literature on the endocrine factors that may be operative in criminality. The work includes chapters on the anthropology of the criminal; general endocrine data pertaining to the thesis; the relation of endocrinology to morphology, psychology, pathology, criminology in general, sexual manifestations and delinquencies; and the medico-psychological examination of criminals. The book closes with a unique bibliography of ten pages.

The work is one that must command the attention of all who are seriously engaged in a study of the biology of criminality. Such workers will find a large body of data brought to a focus on their problems.

## Abstract Department

Note on the asthenia following decapsulization (*Sur l'asthénie consécutive à la destruction des glandes surrénales*). Abelous, J. E. and H. Lassale, *Compt. rend. Soc. de biol.* 101: 998. 1929.

In decapsulated toads and frogs there is a disturbance of the response of nerve and muscle to electrical stimuli, heterochronism. This is due to the curare-like effects of the poisons which accumulate when the adrenals are lacking.—J. C. D.

Effects of long continued administration of adrenalin. Affleck, A. M., *J. Pharmacol. & Exper. Therap.* 36: 301. 1929.

Rabbits tolerated daily injections of adrenalin up to 2 mgm. as long as 120 days, as indicated by failure to alter the curve of hyperglucemia.—C. I. R.

Influence of glycerine extracts from adrenals of rabbits with epithelioma on the evolution of this experimental epithelioma in white mice (*Modifications évolutives de l'épithélioma expérimental de la Souris blanche par injection d'extraits glycélinés de surrénales provenant de Lapins préparés avec ce même épithélioma*). Arloing, F., A. Jossierand and J. Charachon, *Compt. rend. Soc. de biol.* 101: 1140. 1929.

Such extracts when injected daily arrested the growth of the tumor. Extracts from uninoculated rabbits were ineffective.—J. C. D.

Pathologic anatomy in twenty-eight cases of Addison's disease. Barker, N. W., *Arch. Path.* 8: 432. 1929.

During the past eighteen years at the Mayo Clinic necropsy has been performed in twenty-eight cases in which the clinical syndrome of Addison's disease has been present. The protocols of these cases were reviewed and all the material available was re-examined. In twenty-five of the twenty-eight cases there was a lesion of the suprarenal glands which on histological examination was called tuberculosis. In the sections of all these cases there were typical areas consisting of tubercles with endotheloid cells, giant cells, fibroblasts and lymphocytes. Acid-fast bacilli morphologically resembling bacilli of tuberculosis were found in these sections in eleven cases out of the fourteen cases in which the necropsy was done in 1925 or later. Acid-fast bacilli were not found in sections of the suprarenal glands from necropsies done prior to 1925. The tuberculosis of the suprarenal glands was found to be bilateral in all of the twenty-five cases and involved the entire gland with almost complete destruction. Some cortical tissue was found in all of the twenty-five cases except one in which there was incomplete material for study. This remaining cortical tissue was seen only as small islands or as cortical adenomas. The amount of suprarenal cortical tissue remaining was always very small compared to the normal amount and was estimated as less than 5% of this. The remaining three of the twenty-eight cases of Addison's disease which were studied had advanced atrophy of the suprarenal glands. Healed tuberculosis lesions of the lungs were found in all the cases in which there was tuberculosis of the suprarenal glands. Active tuberculosis of other organs was found in twenty-two of these. The weight of the heart was less than the average normal in fourteen of twenty cases in which data on the weight of the heart was available. Diffuse degenerative changes in the renal tubules were present in nine cases. In ten cases, including the three cases of suprarenal atrophy, the thymus was enlarged and there was hyperplasia of lymphoid tissue in the nodes and intestinal tract. There was scattered lymphoid hyperplasia in eight other cases. Seventy-three cases in which there were suprarenal lesions but in which clinical evidence of Addison's disease was lacking were briefly presented. These included the following: primary suprarenal neoplasms, fifteen cases; secondary suprarenal neoplasms, thirty-nine cases; atrophy, two cases; amyloidosis, three cases; infarction, two cases; hemorrhage, three cases; abscess, one case, and tuberculosis with incomplete destruction, eight cases.—Author's Abst.

Addison's disease. Bell, H. J., Penn. Med. J. 33: 391. 1930.

The patient described was a white male aged 28. On May 1, 1929, he was seized with an attack of acute pain over the right costal margin extending into the right shoulder and lasting a few hours. Immediately afterward relatives and friends observed that he was developing what they described as "bad color." Several days later there occurred gastro-intestinal discomfort, anorexia, nausea, irregular attacks of vomiting, diarrhea and vertigo. The bad color continued to increase and deepen. On physical examination the patient, who in good health weighed between 160 and 170 lbs., was reduced to 147. The skin was dry and presented a distinct smoky hue in irregular patches covering his face, hands, back and about both axillae. The abdomen was retracted. The tongue was heavily coated; temperature was 96° F., the pulse rate 76. The systolic blood pressure was 78, the diastolic 56. A tentative diagnosis of Addison's disease was made. During the next two weeks the symptoms, particularly those referable to the gastro-intestinal tract, persisted without response to efforts directed toward their relief. The weakness became increased, the color of the skin deepened, and on July 13, following progressive intensification of subjective and objective symptomatology, death occurred from exhaustion. Autopsy was refused.—I. B.

Relation between the effects of adrenin on the arterial pressure and the place of injection (peripheral veins, portal vein and peripheral arteries) (*Action de l'adrénaline sur la pression artérielle et lieu d'injection veins périphériques, veine-porte et artères périphériques*).

Changes in glycemia and the white blood cells following injection of adrenin into the circulation (*La glycémie et le comportement des globules blancs du sang périphérique après injection d'adrénaline dans la circulation*). Borysiewicz, A., *Compt. rend. Soc. de biol.* 102: 97, 99. 1929.

Injection into a vein, peripheral or portal, of dogs is followed by a rise in blood pressure, while no such rise follows introduction in a peripheral artery. Increase in blood sugar and in number of white corpuscles follow the introduction of adrenin regardless of the site of injection, though the results are not identical. These results show that adrenin is not destroyed by the liver or the cells of the peripheral tissue, but is lost passing through the capillaries.—J. C. D.

Absorption of epinephrine from the subcutaneous tissue of the rat. Cori, C. F. and G. T. Cori, *Proc. Soc. Exper. Biol. & Med.* 27: 558. 1930.

Intravenous injections of 0.001 mgm. of epinephrine per kilo per minute were always followed by a rise in blood pressure in amytal anesthetized rats. Subcutaneous injection of 0.2 mgm. per kilo made shortly afterwards had no effect on blood pressure but did produce hyperglycemia. The rate of absorption from the subcutaneous tissue of the rat must thus be less than 0.001 mgm. per kilo per minute, and greater than 0.0002 mgm. per kilo per minute, since this amount intravenously is the smallest amount which produces hyperglycemia in rats. By extraction of the subcutaneous tissue at the site of an injection and testing for epinephrine content by the Folin-Cannon-Dennis method it was found that epinephrine was still present 3 hours after the injection. Hyperglycemia also persists for at least 3 hours.—M. O. L.

The replacement of depleted adrenalin in the suprarenals. Crawden, G. P., *J. Physiol.* 68: 313. 1929.

After depletion of adrenalin by cold, restoration in both normal and denervated glands proceeds at an equal rate. Nervous control is not necessary for recovery.—C. I. R.

A comparative study of the effect upon rat and rabbit tissue of ephedrine sulphate, epinephrin hydrochloride and an adrenalin-like substance. Doty, E. J., *J. Pharmacol. & Exper. Therap.* 36: 519. 1929.

The adrenalin-like substance was identical with epinephrine except for the absence of one hydroxyl group. No gross or microscopic pathology was discovered in any of the animals after prolonged administration.—C. I. R.

The hormone of the adreual cortex. Hartman, F. A. and Katherine A. Brownell, *Proc. Soc. Exper. Biol. & Med.* 27: 938. 1930.

Hartman reports further characteristics and properties of his extract of adrenal cortex by the use of which completely adrenalectomized cats may be kept alive in good condition indefinitely. In one cat receiving an inadequate supply of the extract the final stages of prostration, with dyspnea and convulsive twitchings had developed. Within 100 minutes after a dose of the extract the animal had recovered sufficiently to eat its usual quantity of food.—M. O. L.

Report of a case of paroxysmal hypertension cured by removal of an adrenal tumor. Porter, M. F. and M. F. Porter, Jr., *Surg. Gynec. Obstet.* 50: 160. 1930.

This is apparently the second case reported in which diagnosis was made before operation. Malignant invasion of chromaphil-cell tissue seems to lead to hyperfunction.—A. T. C.

On the function of the adrenals. Rogoff, J. M., *Endokrinologie*, 5: 256. 1929.

The author reviews the work of himself and colleagues which he interprets as contravening the idea that the adrenal medulla has any significant function. His work, however, is in accord with that of others as indicating an important function for the cortex. He suggests renaming the hormone of the adrenal cortex "interrenalin" and reports successful efforts to obtain an active extract containing this hormone.—R. G. H.

Adrenal extracts as regulators of iron metabolism (*L'extrait de surrénales régulateur du métabolisme ferrique*). Sokoloff, B., *Compt. rend. Soc. de biol.* 101: 1098. 1929.

Iron combined by dialization with extract of the entire adrenal had a stimulating and regulating effect in dilute solutions on the regeneration of certain infusoria, but in concentrated solution produced liquefaction of the cytoplasm.—J. C. D.

The action of ephedrine, pseudoephedrine and epinephrine on the bronchioles. Swanson, E. E., *J. Pharmacol. & Exper. Therap.* 36: 541. 1929.

Changes were recorded by an intrathoracic plethysmograph in pithed dogs. The three drugs produced broncho-dilatation which was not abolished by ergotoxin, ergotamine or atropine.—C. I. R.

An aqueous extract of the suprarenal cortex which maintains the life of bilaterally adrenalectomized cats. Swingle, W. W. and J. J. Pfiffner, *Science*, 71: 321. 1930.

This preliminary report indicates that the authors have succeeded in obtaining a satisfactory extract. Its preparation is described.—R. G. H.

Further observations on adrenalectomized cats treated with an aqueous extract of the suprarenal cortex. Swingle, W. W. and J. J. Pfiffner, *Science*, N. S. 71: 489. 1930.

The authors report further strikingly successful work with their cortical extract. Epinephrectomized cats have maintained perfect health up to 100 days of age, then upon discontinuance of the extract have soon developed acute, fatal adrenal deficiency. Other animals allowed to develop pronounced signs of deficiency immediately after adrenal excision have within four days been restored to health. The extract is stable in benzene or alcoholic solution.

—R. G. H.

Comparative effects of ephedrine and epinephrine on blood pressure, and respiration with reference to their alteration by cocaine. Tainter, M. L., *J. Pharmacol. & Exper. Therap.* 36: 569. 1929.

Responses to ephedrine tend to decrease with successive doses, while the responses to epinephrine tend to increase.—C. I. R.

Glands of internal secretion and dementia praecox (*Contribuição para o estudo das glandulas de secreção interna na demencia prococe*). Cesar, O., *Memo-rias do Hospital de Juquery, S. Paulo, Brazil, 5-7: 119. 1929.*

The author studied at post mortem the endocrine glands of 11 subjects of dementia praecox of whom 7 had died of pulmonary tuberculosis, 2 of enteritis, 1 of pneumonia and 1 of dysentery. The ages ranged from 26 to 46 years. The material was fixed in formol or Bouin's fluid. Various routine stains were used. Results: In general the thyroid showed sclerosis, adenomas or colloid goiter; the testes, sclerosis, diminution of interstitial cells and absence of spermatogenesis; the adrenals showed no systematic alterations though the majority showed augmented lipoids.—R. G. H.

**Endocrine factors in dermatoses. Various Authors.**

An interesting series of abstracts on this general topic is published in *Endokrinologie, 6: 148. 1930.*—R. G. H.

**Sex differences in the cholesterol content of tissues.** Chamberlain, E. N., *J. Physiol. 68: 259. 1929.*

The cholesterol content of the suprarenals, ovaries, spleen, kidney, liver and brain were determined in rabbits of both sexes. Ten of the 19 females were pregnant from 6 to 28 days. The results were inconclusive for all the organs except the suprarenals and ovaries. Normal females showed an average of 66% more cholesterol in the suprarenals than the males. In pregnancy this excess largely disappeared. The ovaries were very rich in cholesterol but the percentages in pregnant and non-pregnant animals were about equal, but the absolute amounts must have been greater in the pregnant females since the ovaries averaged more than twice the weight of those of non-pregnant females. The author suggests that cholesterol is elaborated by the suprarenals of females in order to meet special requirements of pregnancy in building new tissue and that the ovaries supplement this function.—C. I. R.

**Endocrinologic interpretation of normal weight, height and proportions.** Engelbach, W., *Endokrinologie, 5: 28. 1929.*

A valuable compilation of data on human growth, size, proportions and ossification at different ages. It can not be adequately abstracted.—R. G. H.

**The relation of endocrine organs to polyglobulia, and a clinical type, probably of hormone origin** (*Über die Beziehung endokriner Organe zur Entstehung der Polyglobulie und über klinische Typen hormonal bedingter Polyglobalie*). Gunther, H., *Endokrinologie, 4: 96. 1929.*

Endocrine glands, according to their ability to increase the number of the red corpuscles, are arranged as follows: suprarenals, sex glands, hypophysis, thyroids, adrenal organ and spleen. Clinical conditions make it difficult to determine the part each plays since they are interacting. The second part of the paper is given over to a discussion of the hyper-suprarenalism, cases of which were observed. Most of these, including both male and female patients, showed an excess of red corpuscles. There is therefore probably a relationship between the suprarenal and polyglobulia.—B. C.

**Physiology of the corpus luteum. VI. The production of progestational proliferation of the endometrium of the immature rabbit by progestin** (an extract of the corpus luteum) after preliminary treatment with oestrin. Allen, W. M., *Am. J. Physiol. 92: 612. 1930.*

Progestational proliferation can be induced regularly in the uterus of the immature rabbit weighing from 575 to 1647 grams by the injection of progestin if the uterus is first brought under the influence of oestrin. If, however, the animals are not treated with oestrin before the administration of progestin, only a very small percentage of them respond to progestin treatment.

—Author's Abst.

Studies on the influence of castration on the anal scent glands in rabbits (*Étude de l'influence de la castration sur les glandes anales odorantes du Lapin*). Badesco, M., *Compt. rend. Soc. de biol.* **102**: 527. 1929.

These glands are present but differ in appearance in the two sexes. Castration causes a change toward an indifferent type of gland, so that those of the castrated male and female resemble one another closely.—J. C. D.

The valuation of the ovarian hormone (folliculin) (*Sobre la valoración de la hormona ovarica [folliculina]*). Banti, L., *Rev. sud-am. de endocrinol.* **12**: 767. 1929. *Abst., Chem. Absts.* **24**: 1150.

The ovarian hormone is soon destroyed in the organism. Repeated very small doses are better for producing estrus in the spayed rat than few larger injections. As solutions in oil are slowly absorbed, generally fewer injections are sufficient, but this cannot be established as a rule. To adapt the test to conditions for the practical use of the preparation, the suggestion is made to give H<sub>2</sub>O and oil solution in three injections at intervals of 24 hours.

The endocrine activity of the ovaries and disturbances of the menopause (*L'activité endocrinienne des ovaires et les troubles de la menopause*). Béclère, A., *Presse méd.* **37**: 1363. 1929.

The temporary or final cessation of the endocrine function of the ovaries causes the appearance of the disturbances of the menopause. Simple amenorrhea without any other trouble than the absence of the menstrual flow is compatible with and often exists with the persistence of the endocrine function of the ovaries. Amenorrhea with menopausal disturbances is a sure sign of the temporary or final cessation of this function.—J. Gagnon.

Note on the physiological properties of corpus luteum extract (*Contribution à l'étude des propriétés physiologiques des extraits de corps jaune*). Brouha, L. and H. Simonnet, *Compt. rend. Soc. de biol.* **101**: 366. 1929.

A water soluble lipid free extract of corpora was used. In selected doses it suppressed the oestrous cycle in rats, while in smaller doses it produced changes similar to pseudogestation. It had no influence on the genital tract of spayed animals. If it was injected in spayed females after a dose of folliculine large enough to re-establish the oestrous cycle, it nullified the effect of the folliculine. If both extracts were injected simultaneously, the corpus luteum extract had no effect on the stimulating influence of the folliculine.—J. C. D.

On the clinical use of the ovary-stimulating hormone of the placenta. Preliminary report. Campbell, A. D. and J. B. Collip, *Canad. M. A. J.* **22**: 219. 1930.

Using the placental hormone preparation described in a previous paper in selected cases of ovarian hypofunction, definite results of an encouraging character have been obtained in five cases of oligo-menorrhoea, two cases manifesting distressing menopausal symptoms, and in two of dysmenorrhoea. A case exhibiting menopausal symptoms after pan-hysterectomy received no benefit.—A. T. C.

The development of the right gonad of the domestic fowl after ovariectomy; its physiological consequences (*L'évolution de la gonade droite de la poule domestique après ovariectomie; ses conséquences physiologiques*). Caridroit, F., *Am. J. Physiol.* **90**: 307. 1929.

The normal domestic fowl has only one ovary situated in the left side of the abdomen. The complete removal of the ovary makes a neutral animal with a cock's plumage but with the small comb, and spurs of the hen. Ovariectomy of the fowl often has as a consequence the development of the right gonad, which has remained in an embryonic state, into a testicle or less frequently an ovari-testicle. The bird in the latter case presents the appearance of a true gynandromorph with the hen's plumage and the cock's comb, if the necessary tissues are present in sufficient quantities.—J. Gagnon.

Sex hormones of the female. A review. Collip, J. B., *Canad. M. A. J.* **22**: 212. 1930.

The review deals with oestrin of the ovary, the control of ovulation by the internal secretion of the anterior lobe of the pituitary, and the possible occurrence of internal secretions in the placenta.—A. T. C.



**The ovary-stimulating hormone of the placenta.** Preliminary paper. Collip, J. B., *Canad. M. A. J.* **22**: 215. 1930.

At B. P. Wiesner's request, Collip undertook the further purification of the former's sulphosalicylic acid extract of placenta, and has succeeded in obtaining micro-crystalline fractions of great potency, although it is still uncertain whether they are a pure chemical compound. The preparation is active by oral administration in dosage which is not more than two or three times the effective subcutaneous dose. It does not appear to be destroyed by peptic or tryptic digestion in vitro. Immature white rats are stimulated by this preparation to oestrus, which then usually becomes cyclic. Injection into adult castrates is without effect, and injection into adult vigorous normal females has little effect on the normal oestrus cycle. Injections of moderate doses into pregnant rats do not affect the normal termination of pregnancy; this negative result may be due to size of dose and the point is being further investigated. The results suggest that in clinical use only those individuals showing definite evidence of hypoactivity of the ovary may expect to receive benefit from this placental hormone. It is considered probable that the hormone is elaborated in the placenta and is not the internal secretion of the anterior pituitary simply stored in the placenta.—A. T. C.

**The psycho-physiology of a castrated dog** (*Sur la psycho-physiologie du chien privé de testicules*). Combemale, P., *Compt. rend. Soc. de biol.* **101**: 1133. 1929.

This is a description of the differences, including lack of aggressiveness, jealousy, and boisterousness, as seen in dogs where both castrate and litter mate control were living in the house as pets.—J. C. D.

**Isolation of the relaxative hormone on the corpus luteum.** Fevold, H. L., F. L. Hisaw and R. K. Meyer, *Proc. Soc. Exper. Biol. & Med.* **27**: 604. 1930.

**Purification of hormone of corpus luteum responsible for progestational development and other reactions.** *Id.* 606.

Procedures are described for the extraction, separation and partial purification of 2 hormones of the corpus luteum; one causing relaxation of the pelvic ligaments and the other causing inhibition of ovulation, vacuolation of the vaginal mucosa in rats and the production of the premenstrual endometrium in monkeys.—M. O. L.

**The position of the ovarian hormone in the hormone series** (*Über die Stellung des Ovarialhormones in der Hormonreihe*). Csepai, K., A. Fornet and S. Pellathy, *Endokrinologie*, **3**: 361. 1929.

Clinical studies of menformon which is presumed to contain the ovarian hormone indicate that the ovarian hormone is more nearly like insulin than adrenalin since it decreases the sympathetic tonus, blood sugar, and blood pressure.—B. C.

**Female sex hormone.** Frank, R. T. and M. A. Goldberger, *J. A. M. A.* **94**: 1197. 1930. *Abst., A. M. A.*

Frank and Goldberger assert that a lower renal threshold has been demonstrated for the excretion of the female sex hormone in amenorrhea and functional sterility, and evidence is adduced suggesting the existence of a general law governing the urinary threshold excretion of all hormones.

**The male hormone.** Funk, C., B. Harrow and A. Lejwa, *Am. J. Physiol.* **92**: 440. 1930.

The urine of young men contains a hormone (or hormones?) which induces comb growth in capons when a properly prepared extract of such urine is injected. The extracts obtained from testicles, when injected, also give definite but less marked effects. The difference may depend upon the amount of material used. Administration per os also has some effect, but the effect is much less pronounced and less constant than when the extract is injected. The male and female hormones show marked similarity in chemical properties. Both may be extracted with chloroform; both form alkaline salts; both are found in the fatty acid fraction; and the methods of purification so far adopted apply to both hormones.—Authors' Summary.

The results of testicular transplantation in Brown Leghorn hens. Greenwood, A. B. and J. S. S. Blyth, *Proc. Roy. Soc. B.* 106: 189. 1930.

Both of the testes from a brother or chick of approximately the same age were implanted into a female of 6-39 days of age. The grafts were placed in a cavity between the anterior end of the kidney and the ribs. Of the 17 birds which received transplants, 10 showed no change except transient modifications. In 5 of the birds the combs resembled those of a juvenile male, spurs were developed, and plumage assumed the juvenile male type. The shape of the eggs laid by one of the groups (2 birds) was abnormal, the eggs being long and thin.—E. L.

Cowper's gland as a testis hormone indicator. Heller, R. E., *Proc. Soc. Exper. Biol. & Med.* 27: 751. 1930.

The use of Cowper's gland in castrated rats is suggested as a qualitative indicator for testis hormone. Castration has a marked effect on Cowper's gland. In the rat after 20 days castration, a degeneration and merging together of most of the tubules and a lowering of the epithelium occurs, after 60 days there is a marked decrease in the gross size. Injection of testis extracts gave notable effects, including a return of the epithelium to the normal type. Relatively large amounts of hormone were necessary to keep the glands in normal condition.—M. O. L.

Production of a premenstrual endometrium in castrated monkeys by ovarian hormones. Hisaw, F. L., R. K. Meyer and H. L. Fevold, *Proc. Soc. Exper. Biol. & Med.* 27: 400. 1930.

Five sexually mature female monkeys were castrated and then brought into full oestrus by the injection of follicular hormone. Such animals do not show the typical premenstrual development of the uterine endometrium. The additional injection of corpus luteum extracts, however, produced typical premenstrual changes in the endometrium.—M. O. L.

A forty-eight hour test for the female hormone with capon feathers as indicator. Juhn, Mary and R. G. Gustavson, *Proc. Soc. Exper. Biol. & Med.* 27: 747. 1930.

The possibility is suggested of using as a test for the female hormone, the appearance of pink pigment at the base of the breast feathers of capons (the pigment is normally black in the species used) as a response to the hormone.—M. O. L.

Effect of serum from pregnant women on the estrual cycle of the guinea pig. Kelly, G. L. and L. Florence, *Surg. Gynec. Obst.* 50: 435. 1930.

On the belief that during pregnancy there is an excess of corpus luteum hormone over the estrus-producing hormone in the circulating blood and on the basis of knowledge that estrus is inhibited by the corpus luteum hormone, experiments were undertaken to learn whether injections of serum from pregnant women would delay the onset of estrus in the guinea pig. Three groups of animals were used, the first as test animals and the other two as controls. The latter two received respectively serum from nonpregnant women and 1% peptone solution. The amount of serum injected in the first two groups varied from a total of 12 cc. to 20 cc., given over four days with increasing dosage daily. The third group received 20 cc. of peptone solution in four days. In the first group (test animals), there was a delay of from three to eight days in the onset of estrus, with an average of six days. In the second group the postponement was from 0 to two days, with .8 average. In the peptone group there was no delay. No effort has as yet been made to determine whether the effects vary if the serum is obtained from women in early, middle or late pregnancy.—G. L. Kelly.

Basal metabolism and other observations following oestrin injections. Kunde, M. M., F. D'Amour, A. J. Carlson and R. G. Gustavson, *Proc. Soc. Exper. Biol. & Med.* 27: 745. 1930.

Oestrin was prepared from urine of pregnant women and injected subcutaneously into 2 normal and 2 spayed female dogs in doses of 100 or 200

rat units for period of 10 to 39 days. The basal metabolic rate determinations were all within normal limits of variation. Congestion and enlargement of the external genitalia and hemorrhagic discharge from the vagina were observed in all 4 dogs, as was also mating behavior and copulation.—M. O. L.

**Results of castration on the secondary sex characters of the guinea pig** (*Effets de la castration sur les caractères sexuels secondaires du Cobaye*). Guimaraes, A., *Compt. rend. Soc. de biol.* 102: 250. 1929.

The external genitalia, the body size, and psychic of a grown male guinea pig remained normal for a year and a half following castration. On autopsy no traces of testicular tissue could be found.—J. C. D.

**Therapeutical experiments on females with spontaneous dysgenesis** (*Experimentell-therapeutische Studien an Weibchen mit spontaner Zyklusinsuffizienz*). Loewe, S. and H. E. Voss, *Endokrinologie*, 3: 343. 1929.

A condition previously reported as hypohormonic occurs in laboratory animals, particularly white mice. It can be relieved by a diet of ground oats, rye bread and "promonta," a commercial product containing vitamins, lipoids, etc. The presence of the disease is evidenced by cessation of oestrus; its relief by recurrence of oestrus.—B. C.

**Effect of lutcin feeding on the oestrus of the guinea pig.** Macht, D. I. and A. E. Stickels, *Proc. Soc. Exper. Biol. & Med.* 27: 427. 1930.

A series of guinea pigs were fed daily from 0.1 to 0.2 grams of desiccated corpus luteum substance from sows. There occurred definite inhibition of the oestrous cycles, with shortening of the oestrus and lengthening of the dioestrus periods.—M. O. L.

**Experimentally induced intermenstrual bleeding in ovariectomized monkeys.** Maddux, W. P., *Proc. Soc. Exper. Biol. & Med.* 27: 873. 1930.

In 2 adult ovariectomized macaques bleeding was observed in the vaginal smear on the tenth to twelfth days of treatment with ovarian hormone given intravaginally in gelatine pessaries.—M. O. L.

**Preconception ovarian radiation: Its influence on the descendants of the albino rat.** Murphy, D. P., *Surg. Gynec. Obst.* 50: 588. 1930.

A group of 51 albino rats was exposed to heavy ovarian radium treatments, before they were mated. Each of these animals later cast one or more litters. The total first generation young amounted to 402. Of these, 17 females gave birth to 91 offspring (second generation), after mating with brothers, or with males born of other irradiated mothers. No instance of abortion was observed in either generation. In the irradiated animals either sterilization resulted or else the treatment did not materially alter the frequency with which subsequent conceptions followed one another. Litter size was diminished by maternal ovarian irradiation, the earliest litters being the smallest. The first generation young exhibited a delay in growth and fertility but presented no gross abnormalities which could reasonably be ascribed to the effect of the maternal irradiation. Likewise the second generation of offspring showed no evidence of ill health or underdevelopment which might be attributed to the grandmaternal irradiation.—Author's Summary.

**The prolongation of pregnancy by extracts of corpus luteum.** Nelson, W. O., J. J. Pfaffner and H. O. Haterius, *Am. J. Physiol.* 91: 690. 1930.

Extracts of corpora lutea of pregnancy (sow) were successful, when administered subcutaneously, in prolonging the period of pregnancy in rats (13) for periods ranging from 30 to 150 hours. The young born 40 hours or more overtime gave evidence of a size larger than is characteristic of a pregnancy of normal duration. If the period of prolongation did not exceed 70 hours, the young were viable when born. In excess of this time still births occurred.—Authors' Summary.

Ovarian transplantation (with a report of thirty-one cases). Norris, C. C. and C. A. Behney, Surg. Gynec. Obstet. 49: 642. 1929.

Ovarian transplantation is not a substitute for conservation of the ovary in its normal situation and should be reserved for those cases in which this is inadvisable. The life of a transplanted ovary is probably not more than 2 or 3 years. Grafts frequently become tender for a day or two each month, but rarely give serious trouble. The operation is practically without mortality or morbidity, and most of the grafts "take." When the menopause occurs it is generally more prolonged, gradual, and analogous to the normal menopause than if grafting had not been performed.—A. T. C.

Recent advances in physiology of menstruation. Novak, E., J. A. M. A. 94: 833. 1930.

The author is of the opinion that radical readjustments must be made in our views as to the physiology of menstruation because of important new developments in this field. There is little doubt that in lower animals the sex cycle can occur independently of ovulation. The best evidence along this line has come from observations on monkeys, which menstruate much as do human females. Menstruation without preceding ovulation is certainly not the rule in women, but there is reason to believe that it occurs at times, though the associated endometrial cycle would naturally be different in such cases. Even if preceding ovulation is the rule, it is not certain that the two are related in the nature of cause and effect. The time has come when the doctrine of the "primacy of the ovum" in the regulation of menstrual periodicity must be abandoned. There is no reason to believe that any other constituent of the ovarian structure is any more important in this respect, but there is evidence to suggest, though not to demonstrate, that the pituitary may, by the probable periodicity of its own function, be the regulator of the menstrual rhythm. This, however, carries the problem only one step toward its solution, for it raises the question of what determines the periodicity of the pituitary, and still leaves the question of menstrual periodicity one of the mysteries of life. The dual nature of the ovarian secretion has been definitely established by the demonstration of an active corpus luteum extract, with properties in some respects antagonistic, in others supplementary, to those of the already well recognized ovarian follicle hormone. For various reasons, especially the fact that the characteristic secretion of the corpus luteum has very different properties from those of the follicle and the placenta, the term "gestational gland," to include these three structures, is incorrect, and should be abandoned. The most important recent contribution to sex physiology, and the one which promises most in its future practical applications, is the discovery that the anterior pituitary constitutes the "motor" of the ovary. The surprising effects of implantations of the anterior lobe on the growth and maturation of the follicular apparatus open up a vast field of possibilities. Although the discovery of the follicle hormone has as yet yielded almost nothing from a therapeutic standpoint, there is reason to feel that the discovery of the underlying role of the anterior pituitary secretion may, in the future, be more productive of results in the treatment of disorders of the sex cycle.—A. M. A.

Concerning the so-called hilus cells of the ovary (Über die sogenannten Hiluszellen des Ovariums). Pawlowski, E., Endokrinologie, 3: 321. 1929.

There are certain cells in the hilus of the functioning ovary which are easily distinguished by their morphology and lipoid content. They are not analogous to the interstitial cells of the testes. Because of their relation to the sympathetic nerves they are supposed to act through them. The name "hilus cells of Berger" is proposed for them.—B. C.

Experimental research on the ovarian hormone (Experimentelle Untersuchungen über die Hormone des Eierstocks). Probstner, A. v., Endokrinologie, 3: 338. 1929.

Oestrus, as determined by vaginal smears in ovariectomized rats, can be initiated by injection of fluid from ripe follicles, glandufolin and folliculine, but not by extracts of ovarian tissue without follicles, or by a number of commercial ovarian preparations. Transplants of human corpora lutea in various stages give positive results, while those of the cow do not. Oestrus is depend-

ent upon a hormone produced by the follicle; this hormone production is hindered by the production of a corpus luteum. In the absence of the hormone menstruation occurs. The periodicity therefore of oestrus depends upon the production of ripe ova. If ripe ova are not present the initiation of oestrus depends upon the introduction of the proper hormone, but if mature ova are present the initiation of oestrus depends upon the ripening time. The addition of the hormone then may only intensify oestrus but can not change its periodicity or rhythm.—B. C.

**Cause of the increased blood pressure at the climacteric (Über die klimakterische Hypertonie).** Rutich, E. v., *Endokrinologie*, 3: 255. 1929.

In order to determine whether or not the increased blood pressure at the climacteric is due to the decrease in ovarian hormone, the author adopted two methods, the clinical-statistical method and the gland therapy method. The glandular substance, menformone, glandufolin, et al., were given by injection. He concludes as a result of both investigations that the cessation of ovarian function is not a primary cause of the increased pressure but that it may be an adjunct in cases where the vegetative nervous system is constitutionally disposed to lability. Glandular therapy has no effect.—B. C.

**Treatment of ovarian insufficiency with sex hormone (Die Behandlung der Ovarialinsuffizienz mit Sexualhormon).** Siebke, H., *München med. Wchnschr.* 76: 1752. 1929.

Two forms of ovarian insufficiency are recognized by the author. The vegetative, representing a failure of maturation of the genitalia and of secondary sexual characteristics, and the generative, irregularity in menstruation due to a derangement of ovulation. On the basis of this classification two tests have been devised in determining the efficacy of any hormonal preparation in the human female. These are the "growth test" by which growth of hypoplastic organs to maturity must be achieved, and the "menstrual cycle test," the institution of a normal menstrual rhythm. Menformon, the preparation selected for this series, was used in 20 cases according to the scheme of dosage worked out by Laqueur. They comprised cases of amenorrhea, metrorrhagia, and dysmenorrhea with or without genital hypoplasia and increasing obesity. As the result of treatment, 12 of these satisfied one or both tests with alleviation of symptoms. They included 4 amenorrheas. Of the failures 5 were obese individuals showing stigmata of pluriglandular disturbances and in these anterior lobe pituitary hormone (prolan) also was ineffectual. In 1 case the growth test was positive but the symptom of which the patient complained, dysmenorrhea, was not helped. The other 2 failures were insufficiently treated and could not be properly controlled. The selection of the proper cases for treatment is stressed. Inflammations, tumors, position changes, and general constitutional conditions must be ruled out. Since cases of pluriglandular disturbances as well are not benefited, the number of cases in which sex hormone therapy is indicated must remain relatively small.—F. Spielman.

**On the reactivation of the senile testis of the rat by means of injections of gonadotrope hormones.** Wiesner, B. P., *Edinburgh M. J.* 37: 229. 1930.

Four animals were used and the result with one of them is given in detail. Injections of the author's protein-free extract of human placenta, or of extracts of cattle anterior lobe, resulted in the apparent return to activity of the prostate and the seminal vesicles, the enlargement of the testis, and the increase therein of the formation of mature spermatozoa. This was checked by removing one testis at the start of the experiment and comparing it with the remaining gland at the end. The author emphasizes the part played by gonadotropic hormones acting on the testis from outside, in cases of rejuvenation.—J. C. D.

**Egg-laying in *Triturus viridescens* following pituitary transplants.** Adams, A. Elizabeth, *Proc. Soc. Exper. Biol. & Med.* 27: 433. 1930.

Female urodeles, *Triturus viridescens*, were caused to deposit eggs out of season by intramuscular or intraperitoneal transplants of whole pituitary or anterior lobe. Posterior pituitary or muscle transplants were without effect.

—M. O. L.

A comparative study of the anterior hypophysis in the pregnant and non-pregnant state. Bacon, A. R., *Am. J. Obst. & Gynec.* 19: 352. 1930.

The hormone content of the anterior hypophysis of pregnant and non-pregnant cattle was compared by transplanting weighed pieces of the glands ranging from 5 to 50 mgm. into infantile female white mice, and comparing the quantity of gland required to produce premature estrus, as determined by vaginal smears (Allen and Doisy's procedure). Contrary to expectations, it was found that the anterior hypophysis of non-pregnant cattle was the more active. The anterior hypophysis of foetal calves had a very low hormone content, only two larger transplants out of 21 being positive. It is concluded that the great increase in anterior pituitary hormone in the circulation during pregnancy in all probability arises elsewhere than in the hypophysis.—Author's Abstract.

Early changes produced in dogs by the injections of a sterile active extract from the anterior lobe of the hypophysis. Benedict, E. B., T. J. Putnam and H. M. Teel, *Am. J. M. Sc.* 179: 489. 1930.

Four dogs were injected with a sterile alkaline extract of the anterior lobe of the hypophysis. Twenty figures of photographs of the animals, their genital tracts and organs are included in the paper. The genital tracts in both male and female were sexually inactive. Skeletal over-growth was produced by daily injections of three months duration. The animals after injection for two months showed sluggishness and a plantigrade stance.—E. L.

The functional significance of the parts of the hypophysis (*Die funktionelle Bedeutung der einzelnen Hypophysenanteile*). Biedl, A., *Endokrinologie*, 3: 241. 1929.

A short survey of the structure and origin of the pituitary with a resume and evaluation of what is known at present about the functioning of the various parts of the gland.—B. C.

On the origin of acroparesthesia (*Über den Ursprung der Akroparästhesien*). Borak, J., *Endokrinologie*, 5: 8. 1929.

Acroparesthesia is a common symptom in acromegaly, in normal menstruation and at the menopause. This condition is amenable to x-ray treatment of the hypophysis. The condition is probably to be ascribed to vasomotor disturbances of hypophyseal origin.—R. G. H.

Effects of hypophyseal and follicular extracts on a young monkey (*Action des extraits hypophysaire et folliculaire chez la Guenon impubère*). Courrier, R., R. Kehl and R. Raynaud, *Compt. rend. Soc. de biol.* 101: 1093. 1929.

Signs of precocious oestrous cycles were produced by injection of extract from beef hypophysis and by folliculine in a two-year-old macacus sylvanus. —J. C. D.

Chondrodystrophia (*Über Chondrodystrophie*). Curschman, H., *Endokrinologie*, 4: 161. 1929.

The author cites three cases of dwarfs, two of which are normal in general except for size. He is unable to account for them on hormonal basis. The sella turcica in each appears normal. He suggests that inheritance may be a factor, but is really at a loss to explain the cause of dwarfism. The third has excessive fat which is considered as a "coincidence."—B. C.

Contribution to the anterior hypophyseal reaction with special consideration of the Aschheim-Zondek pregnancy reaction (*Beitrag zur Hypophysen-Vorderlappen-reaction unter Besonderer Berücksichtigung der Aschheim-Zondekschen Schwangerschaftsreaktion*). Ehrhardt, K., *Klin. Wchnschr.* 8: 2044. 1929.

In a series of 400 clinically proven cases the Zondek-Aschheim pregnancy reaction was correct within an error of 1.5-2%. Need is expressed for a more

rapid test and the following attempts were made to speed up the reaction: (1) Splenectomy; (2) Removal of one ovary; (3) Removal of one and both uteri; (4) Keeping rats at warmer temperatures. Except for an inhibition of Zondek-Aschheim reaction II and III in (3), the results were essentially negative. Hypophyseal implants were combined with implants of adrenal medulla, cortex of adrenal, whole adrenal, pancreas, pineal body, and thyroid. No definite synergistic or antagonistic action was demonstrated. Prähormon was injected with adrenalin, hypophysin, insulin, and thyroxin. The results are similar to those of the implant experiments. Implanted ovaries did antagonize hypophyseal implants and ovarian extract antagonized prähormon. Anterior hypophyseal hormone is found in the exudate of cantharidin blisters during pregnancy. It was also present in the cerebro-spinal fluid of three patients with eclampsia though not found in the C. S. F. of normal pregnant women. Many other tissues and plants were tested for anterior hypophyseal hormone action with negative results.—D. W. Gaiser.

**Studies of the relation of the pituitary to watermetabolism.** Goldzieher, M. A. and J. Kaldor, *Proc. Soc. Exper. Biol. & Med.* **27**: 799. 1930.

Guinea pigs were given novasurol as a diuretic. They lost 5.2% of their weight in 6 hours as compared with a normal loss of about 3.5%. The pigs were killed from 20 minutes to 6 hours after the novasurol injections and the hypophyses examined histologically. No changes in the structure of the posterior lobe were observed, but in the anterior lobe there was found a decrease in the number of eosinophile cells and of the amount of eosinophile substance, and a marked increase in basophile cells. The same results were obtained with the use of theobromin as a diuretic. The authors interpret these histological changes as indicating stimulation and increased activity of the anterior lobe cells.—M. O. L.

**Growth and bone changes in rats injected with alkaline anterior pituitary extracts.** Handelsman, M. B. and E. F. Gordon, *Proc. Soc. Exper. Biol. & Med.* **27**: 412. 1930.

Rats weighing over 175 grams injected with alkaline anterior pituitary extracts showed good growth response and a greater activity in periosteal bone formation than did their controls. The bone growth reaction consisted of an intensification of the activity of the normal periosteal ossification zones. Those animals that gained most in weight showed the greatest ossification response.—M. O. L.

**Hormones of the anterior pituitary lobe.** Hewitt, L. F., *Biochem. J.* **23**: 718. 1929.

Dilute alkaline extracts were made from beef anterior pituitaries by a method similar to that previously described by Evans and Long in 1923, Teel in 1926, Putnam, Teel and Benedict in 1928, and Bellerby in 1928. Female white rats weighing 128 to 146 gm. were given intraperitoneal injections of 1 cc. each daily. On the average, injected rats grew at the rate of over 12 gm. per week while control animals never grew at a rate exceeding 6 gm. per week. Extracts which were made slightly acid before filtration were variable in growth stimulating properties, one extract producing growth while the next had no such effect. All the extracts, however, stimulated the development of corpora lutea and produced the so-called "mulberry ovary." Beef anterior pituitaries were extracted with N/10 acetic acid, neutralized and filtered. Such extracts had considerable growth stimulating effect upon mature rats but no stimulation of sexual development in immature mice. If the acid extract was shaken well with kaolin and then centrifuged, the supernatant liquid was capable of causing enlargement of uteri and ovaries and cornification of the vaginal mucosa in immature rats. An acid extract made with N/10 hydrochloric acid and shaken up well with kaolin before neutralization and centrifugation was tested on 2 rats. A mature rat showed no stimulation of growth in 2 weeks while an immature rat showed stimulation of sexual development.—E. P. Bugbee.

Effect of pituitary extracts on basal metabolic rate. Himwich, H. E. and F. W. Haynes, *Proc. Soc. Exper. Biol. & Med.* **27**: 815. 1930.

In starved male rats the basal metabolic rate was increased an average of 32% in the first hour after the injection of pitocin and 13% in the second and third hours. Pitressin in doses of 50 to 100 units per kilo decreased the oxygen consumption an average of 22% in the first hour. Variable effects were found with smaller doses. Surgical pituitrin also produced a decrease in oxygen consumption.—M. O. L.

Diabetes insipidus. Jackson, H. B., *Proc. Roy. Soc. Med.* **23**: 74. 1930. (Clin. Sect.)

The patient was a man 34 years old, admitted to the hospital January 31, 1930. His chief complaints were great thirst and frequency of micturition, of 6 months' duration. The frequency occurred diurnally and nocturnally, necessitating his getting up 3 or 4 times during the night. He complained also of becoming "nervy" and excitable. Apart from these symptoms he felt well. He did not suffer from lassitude, weakness, headache, vomiting or visual disturbances. Radiographic examination of the pituitary was negative. The patient responded satisfactorily to subcutaneous injections of pituitrin and one of its components, "vaso-pressin."—I. B.

Histology of the anterior pituitary of the foetal pig with reference to growth and maturity. Nelson, W. O., *Proc. Soc. Exper. Biol. & Med.* **27**: 596. 1930.

Basophile elements greatly predominated in the anterior pituitaries of foetal pigs at about the 10 cm. stage. At about the 20 cm. stage the basophile cells were less numerous than the eosinophils.—M. O. L.

Active principles of pituitary extracts and insulin effect on dogs (*Influencia de las diversas sustancias de la hipófisis sobre la acción insulínica en los perros normales*). Magenta, M. A., *Rev. Soc. argént. de biol.* **5**: 89. 1929.

Oxytocin is the active principle in pituitary insulin antagonism. Vaso-pressin and an anterior lobe extract (Putnam, Teel, and Benedict's technique) does not modify the effect of insulin. Oxytocin causes a rise in blood sugar and the disappearance of symptoms in hypophysectomized dogs with severe hypoglycaemia through insulin injections.

Hormone of anterior lobe of hypophysis: Presence in placenta. Philipp, E., *Zentralbl. f. Gynäk.* **54**: 450. 1930. *Abst., J. A. M. A.* **94**: 1545.

Philipp implanted pieces of amnion, chorion and Wharton's jelly and injected amniotic fluid from pregnant white mice into sexually immature female white mice. In all of the animals the implantation or injection was followed by a hypertrophy of the uterine tubes and the ovaries and the appearance in the latter of a graafian follicle and numerous corpora lutea. The earlier the pregnancy, the more marked were the changes produced. Placental tissue from a mouse in the second month of pregnancy produced much more marked changes than placental tissue from a mouse in the fourth month of pregnancy. In one case, however, an intense reaction was produced by placental tissue from a mouse in the fifth or sixth month of pregnancy. Control experiments with implantations of pieces of fetal organs and umbilical cord tissue all gave negative results. On the basis of his experiments the author concludes that the placenta early in pregnancy contains a large amount of "anterior lobe hormone."

Treatment of pituitary tumors; rôle of roentgen ray and of surgery. Towne, E. B., *Ann. Surg.* **91**: 29. 1930. *Abst. Arch. Physical Therapy*, **11**: 141.

Five cases are reported by Towne which illustrate long-standing favorable results from roentgen treatment, and show that if the result is not good, a cystic tumor, favorable for surgery, may be diagnosed. He believes that the present custom of following surgery immediately with roentgen treatment confuses the issue. The two methods may be used separately without jeopardizing the patient's chance for a cure. He proposes that all pituitary adeno-



mas be treated by roentgen rays under the observation of the ophthalmologist and the neurosurgeon; that the treatment be stopped as soon as improvement begins, and that surgery be undertaken short of six months only when visual acuity and fields recede under roentgen treatment.

**The action of anterior pituitary upon the x-rayed ovaries (*Hypophysenvorderlappenwirkung auf das strahlengeschädigte Ovarium*).** Walter, A., *Endokrinologie*, 7: 1. 1929.

Sixty infantile mice received dosages of 400-500 R and were thereby sterilized. Transplants of anterior pituitary were made from 3-4 weeks after radiation, with oestrus cycles resulting within 80-100 hours. Animals kept for longer periods of time (10-11 grams weight) showed regular oestrus cycles. Transplants in animals 3-4 months old in dioestrus gave excellent results. From these experiments the conclusion is reached that since irradiated ovaries can maintain an oestrus cycle followed by heat, the theca cells must either function as hormone carriers or hormone producers. Since egg cells or fresh corpora lutea can not produce oestrus, the interstitial cells gain in importance. The transplantation is effective only so long as eggs can be produced.—B. C.

**Hormones of anterior lobe of hypophysis (*Ueber die Hormone des Hypophysenvorderlappens*).** Zondek, B., *Klin. Wchnschr.* 9: 245. 1930. *Abst., J. A. M. A.* 94: 1272.

Zondek states that following repeated injections of fluid expressed from the anterior lobe of the hypophysis into rats, Evans observed an enormous growth of these animals. The sex hormone of the anterior lobe of the hypophysis does not have this influence. Consequently the author concludes that besides the sex hormone the anterior lobe of the hypophysis also secretes a hormone that influences the processes of growth. Other investigators observed that the specific dynamic action of food is regulated by the anterior lobe of the hypophysis. It was found that a certain extract of the anterior lobe effected a decrease in the metabolic rate and an increase in the specific dynamic action. The author further discusses the functions of the sex hormone of the hypophysis. Experiments revealed that the sex hormone consists of two different substances. The first one influences the ripening of the follicle. The other substance effects the formation of the corpus luteum. The author gives a diagrammatic sketch showing the action of the four hormones of the anterior lobe of the hypophysis, namely: (1) the hormone affecting growth; (2) the hormone that influences the ripening of the follicle; (3) the hormone that causes development of the corpus luteum, and (4) the hormone influencing metabolism.

**Investigations on functioning of anterior lobe of hypophysis (*Untersuchungen zur Funktion des Hypophysenvorderlappens*).** Zondek, B., *Deutsche med. Wchnschr.* 56: 300. 1930. *Abst., J. A. M. A.* 94: 1451.

Zondek first reviews the results of former researches on the hormones of the anterior lobe of the hypophysis, which were conducted partly by him and partly by other investigators. It has been found that, besides the sex hormone, the anterior lobe of the hypophysis also produces a growth hormone and a substance that influences metabolism. Careful investigations on the action of the sex hormone revealed that it is not an elementary substance but that it contains two factors, the first one effecting ripening of the follicles and the second one effecting luteinization. These two factors are designated as A and B, respectively. Investigation on the pregnancy reaction revealed that the factor A is not characteristic for pregnancy because it may also occur in the urine when pregnancy does not exist. The author succeeded in isolating the A factor of the sex hormone. He asserts that during pregnancy both factors are excreted in the urine in great quantities. However, the A factor occurs alone in the urine when the sex glands do not function properly, namely, after bilateral ovariectomy, and in the menopause. Therefore, the demonstration of this factor in the urine indicates that the sexual function has ceased. Factor A was also found in women with tumors of the genitalia. However, the presence of this factor is not an absolute indication of cancer because it is found also in cases of nonmalignant tumors.

**Surgical treatment of hyperinsulinism.** Allan, F. N. and W. C. Boeck, J. A. M. A. 94: 1116. 1930.

Hyperinsulinism is a condition which may cause serious disability, and sometimes death. When the hypoglycemic tendency is so strong that the patient is incapacitated, surgical treatment is justified. Resection of the pancreas appears to be a logical method of treatment. In one case in which hyperinsulinism was due to tumor of the islands, operation was followed by relief from hypoglycemic symptoms. In four cases in which organic change in the pancreas was not demonstrable, the results of partial pancreatectomy were not entirely satisfactory; yet the improvement observed in three cases was encouraging. Hope of control of the disorder by surgical measures, in such cases, may lie in more radical resection.—Authors' Summary.

**Diabetic coma: A report of eighty-one instances.** Bowen, B. D. and I. Hekimian, Ann. Int. Med. 3: 1104. 1930.

The blood sugar in 64 of these instances varied from 1320 to 266 mgm. It exceeded 400 mgm. in 53 instances. The leucocyte count exceeded 15,000 in 74 of the cases. The treatment consisted of 50 units of insulin subcutaneously and 1000 cc. of salt solution by hypodermoclysis. Sodium bicarbonate, 30-40 grams, was given by mouth or through a stomach tube. Insulin, after the initial dose, was given in doses of 10-30 units every 2-4 hours until the Benedict test solution began to retain some of its blue color. Nearly all the cases of coma showed some degree of circulatory insufficiency, which was treated with caffeine sodium benzoate or a digitalis preparation. Ten of these coma cases died from complications. Abdominal pain was an early symptom of coma. The authors believe that sodium bicarbonate is beneficial in the treatment of coma.—E. L.

**Clinical significance of initial insulin hyperglycemia (Die Glinische Bedeutung der initialen Insulinhyperglykämie).** Bürger, M., Klin. Wchnschr. 9: 104. 1930. Abst., J. A. M. A. 94: 1026.

Bürger points out that it has been demonstrated that the blood sugar increases during the first twenty minutes following intravenous injection of insulin. This initial insulin hyperglycemia is especially marked if the insulin is injected directly into the portal vein or into one of its branches. However, if the liver circulation has been interrupted and insulin is injected into a peripheral vein, the initial insulin hyperglycemia does not develop. The author describes experiments on several groups of persons. Tests on healthy persons without disturbances of the liver revealed that after the insulin injection the sugar content of the blood was on the average 22% higher than before the injection. In patients with cirrhosis the initial insulin hyperglycemia reached only 2.7%, and in some instances it was entirely absent. Patients with severe cholemia showed an increase of only 5.7%, whereas in persons who had recovered from jaundice and in whom the bilirubin content of the blood was normal, the primary insulin hyperglycemia reached 14.5%. These tests prove that the development of initial hyperglycemia depends on the condition of the parenchyma of the liver. However, experiments on animals proved that it was also necessary that the glycogen depots of the liver should be full. Starving animals developed only a minor initial hyperglycemia. In patients with hyperthyroidism the primary insulin hyperglycemia was considerably less than in persons with a normal basal metabolism, whereas in patients with myxedema the initial hyperglycemia was in excess of that in healthy persons. In one individual with myxedema it was 70% higher than the sugar content before the insulin injection. The author reasons that in patients with hyperthyroidism the glycogen depots are exhausted as a result of an increased metabolism. On the other hand, in patients with hypofunctioning of the thyroid, there is an oversupply of glycogen because the metabolic rate is reduced. The author also examined patients with diabetes. He found that in those who previously had received insulin treatments and who adhered to a restricted diet the primary hyperglycemia was about like that in normal persons. In patients with diabetic coma, however, it was absent. It is assumed that this is due to the deficient glycogen content in the liver of comatose persons. In conclusion the author stresses that all these experiments were made with the same brand of insulin. Tests with other brands are now being conducted and it appears that the pharmacologic properties are not the same in all brands.

The effect of shivering on respiratory quotient in pancreatic diabetes. Chai-koff, I. L. and J. J. R. MacLeod, Quart, J. Exper. Physiol. 19: 291. 1929.

Dogs were completely depancreatized and maintained in good nutrition by feeding raw meat, raw pancreas and cane sugar, with insulin injections twice daily. After operation recovery, food and insulin were discontinued for a few days and resting metabolism determined. Then while the animal was shivering from a cold bath it was placed in a cabinet cooled to 10° to 13° C., and metabolism again determined. Normal fasting controls were similarly treated. In both groups oxygen consumption and the respiratory quotient were increased to about an equal degree. The high quotient was proven not to be due to discharging CO<sub>2</sub> combining power of blood before and during shivering. That protein metabolism was not increased was determined by urinalysis. It was concluded, therefore, that the high quotient was due to oxidation of carbohydrate which was not accompanied by gluco-neogenesis from fat. The failure of the quotient to remain high during the entire shivering period supports this conclusion. That the falling of the quotient was not due to decreased metabolism was indicated by the sustained increase in oxygen consumption. Carbohydrate can be utilized by both normal and diabetic dogs.—C. I. R.

The use of constant glucose injections for the study of induced variations in carbohydrate metabolism. II. The effects of insulin, pancreatectomy and nervous manipulations of the pancreas. Colwell, A. R., Am. J. Physiol. 91: 679. 1930.

The administration of insulin diminishes, and of epinephrine increases, the excretion of sugar resulting from the constant injection of glucose by vein. With proper dosage these responses may occur with no corresponding changes in the blood-sugar concentration. Complete removal of the pancreas causes virtually all of a constant supply of glucose to be excreted in the urine. The effect appears gradually over a period of four to eight hours. Under amytal anesthesia the ability to utilize glucose is not impaired by stimulation of the major splanchnic nerve after removal of the corresponding adrenal gland and section of the hepatic nerves, by denervation of the pancreas, or by bilateral vagus section.—Author's Summary.

The use of constant glucose injections for the study of induced variations in carbohydrate metabolism. III. The fate of the retained sugar under normal conditions and after epinephrin and insulin. Colwell, A. R. and E. M. Bright, Am. J. Physiol. 92: 543. 1930.

Working on cats under amytal anesthesia it was found that when glucose is administered intravenously at constant rates high enough to cause abnormal glycosuria, after the first three or four hours a constant proportion of it (usually about three-quarters under the present conditions) can be accounted for by oxidation and excretion, and occasionally also by conversion to fat. Two implications may be made from this fact: (a) glycogen storage eventually proceeds at a constant measurable rate; (b) after the initial period of adjustment of free sugar concentration in the tissues, all administered glucose not utilized is excreted promptly in the urine. Evidence is presented which indicates that insulin results in a transient increase in sugar combustion and a more prolonged augmentation of the rate of glycogen storage, and that epinephrin causes a net loss of glycogen from the body. Glucose oxidation is abolished by prolonged administration of epinephrin intravenously at a rate of 0.001 mgm. per kgm. per minute. This occurs in spite of a constant intravenous supply of glucose. Since glucose oxidation invariably occurs under identical conditions without epinephrin, the use of anesthesia in the present investigations is in no way responsible for the phenomena. Attempts to reproduce the results of pancreas removal in this manner have been inconclusive. It is not clear, therefore, whether the observed effect of epinephrin is due to a suppression of insulin production or not. Contemporary evidence favors the view that ordinary diabetes mellitus is a result of a functional disorder of the pancreas which is dependent upon a disease of the sympathetic nervous system, and that continuous excessive secretion of epinephrin may be an important intermediate factor in this mechanism.—R. G. H.

A clinical method of insulin assay (Eine klinische method zur Wertbestimmung von Insulin preparaten). Csepai, K. and B. Forstner, *Endokrinologie*, 3: 412. 1929.

A normal person's reaction to insulin varies but little in the course of a few days, and it is proposed to use such an individual for insulin assay in preference to lower animals. Tests with standard solutions are run for three days, then the solution to be standardized is used, and the blood pressure effects compared. This is a desirable method especially where animals are not available.—B. C.

Complications of diabetes. Evans, F. A., *Peun. M. J.* 33: 368. 1930.

The unavoidable complications of diabetes are always serious. Acute general infections carry a double menace—their own and the increased severity of the diabetic state which they invariably induce. With the fever and increased metabolism, perhaps with the over-stimulation of endocrine secretions antagonistic to the islands of Langerhans, sugar tolerance is so depressed that the diabetes can no longer be properly treated by dietary measures alone. Here insulin is practically always necessary. Gastro-intestinal disorders complicating diabetes present to the clinician problems that are usually not serious. Among these are constipation, diarrhea, achylia gastrica and gastric and duodenal ulcers. In these conditions surgical treatment should be instituted promptly and the relief of these complications may assist in the treatment of the diabetes. Thyroid disorders complicating diabetes create discouraging situations since the two conditions, diabetes and thyrotoxicemia, require opposing dietetic management. Senility, myocarditis, chronic kidney lesions, pernicious anemia, arteriosclerosis and such complications as affect the ears, eyes, teeth, genitalia and skin require the indicated corrective measures. Coma is an emergency complication calling for expert attention. Retinitis and lipemia retinalis are relieved promptly with the control of hyperglycemia. Cataract may occur at any age if the diabetes has been relatively severe or of long standing; under insulin treatment some of the lenticular haziness occasionally improves.—I. B.

Essentials for the diagnosis of diabetes mellitus. Jonas, L., *Penn. M. J.* 33: 365. 1930.

The two cardinal objective symptoms in a frank case of diabetes mellitus are glycosuria and hyperglycemia. As a rule, definite subjective symptoms with a glycosuria suggest diabetes. The diagnosis, however, should not depend solely upon glycosuria, for many subjects of glycosuria are non-diabetic. Among these are renal glycosuria and so-called alimentary glycosuria. The differential diagnosis between diabetic glycosuria and non-diabetic glycosuria is often difficult in very mild cases, but a family history of diabetes is significant, although cases of benign glycosuria have been found in families with a marked diabetic history. Generally speaking, the safest procedure when in doubt is to make periodic examination of these patients. In conclusion, Jonas states that there is no single symptom, either subjective or objective, on which the diagnosis of diabetes can be made, with the possible exception of hyperglycemia after fasting from 8 to 12 hours. The sugar tolerance test is the best readily available method for differentiating diabetes from benign glycosuria. Blood sugar within the normal fasting range two hours after taking 100 grams of glucose in untreated cases is evidence that the patient has not diabetes.—I. B.

The significance of ketogenesis. Macallum, A. B., *Canad. M. A. J.* 22: 3. 1930.

Stress is laid on the relative insolubility and non-diffusibility of fatty acids until oxidised to the stage of butyric acid and its oxidation products. The cell-supply of oxygen is limited. Normally simultaneous oxidation of glucose limits the oxygen available for fat, so that so little concentration of butyric acid can occur that it and its products are almost completely oxidised. In diabetic or prolonged fasting conditions nearly all the oxygen reaching the cell is available for fat-oxidation and relatively large amounts of the two ketone-acids are produced, so that considerable quantities may pass into the blood and eventually into the urine. If butyric acid and its products were as little soluble and diffusible as caproic acid and its corresponding oxidation products, glycosuria would occur in diabetes, but no acidosis, and there would be no danger in coma.—A. T. C.

**Functional dysinsulinism with epileptiform seizures.** Nielsen, J. M. and E. L. Eggleston, J. A. M. A. 94: 860. 1930.

Three cases of "epilepsy" due to dysinsulinism or hyposuprarenalism were treated, with frequent feedings or with suprarenal gland or with both, and the attacks of unconsciousness have ceased. In one case there had occurred twelve, in another more than 100, complete seizures with many petit mal attacks; yet all attacks ceased under this treatment. The period of observation in the third case is not yet long enough to justify absolute conclusions. The starvation blood sugar (taken before breakfast one morning) is not always or in all cases an index of the prevailing low point in the patient studied, especially in cases of functional dysinsulinism. In cases of functional dysinsulinism the blood sugar may rise or fall markedly without any premonitory sign that we can at present detect. The degree of increase in blood pressure under the influence of epinephrine is not necessarily any indication that the blood sugar has risen, or vice versa. Frequent feeding alone may suffice in these cases to prevent epileptiform seizures, but frequent feeding plus suprarenal gland by mouth is a surer way of maintaining sufficient blood sugar to prevent attacks. Another group of cases has thus been subtracted from the large unknown group of idiopathic epilepsy, again emphasizing that even in the most hopeless maladies we are never justified in not attempting to give relief. The treatment outlined has had no effect whatever in cases of idiopathic epilepsy.—A. M. A.

**The hypoglycemia hazard in the treatment of diabetes mellitus.** McCrae, T., M. Clin. N. Amer. 13: 1013. 1930.

In certain diabetics hypoglycemia calls for real concern. Children and undernourished adults are most susceptible. On the other hand, permitting hyperglycemia and even glycosuria to continue as a prophylactic of hypoglycemia may make a severe case of diabetes out of a mild one. The level of blood sugar at which hypoglycemia develops varies. While John has found blood sugar within or above normal in 10 patients presenting symptoms of hypoglycemia, Joslin's patient with a blood sugar of .030 per cent was free from complaints. In the average patient, symptoms may be expected when the blood sugar falls below .060 per cent. The factors affecting the level of blood sugar and the insulin requirement are many, the most important being accuracy in diet and insulin administration, infection, acidosis and exercise. The incidence of hypoglycemia is reduced to a minimum and the dangers are practically nil if the simple rules for changing of dosage and distribution of insulin are observed, parallelism of the carbohydrate content of the corresponding meals maintained, and the daily exercise kept nearly uniform in time and amount.—I. B.

**Effect of insulin on alimentary lipemia in normal dogs.** Rony, H. R. and T. T. Ching, Proc. Soc. Exper. Biol. & Med. 27: 533. 1930.

In dogs, both insulin subcutaneously and glucose orally prevented the alimentary lipemia ordinarily occurring after a meal of 2 cc. of olive oil per pound body weight, by stomach tube.—M. O. L.

**Diabetic neuritis with paralysis.** Root, H. F. and M. H. Rogers, New England J. M. 202: 1049. 1930.

Eleven cases of diabetic "neuritis" with motor paralysis as well as sensory symptoms are reported and a classification of the common causes of pain in the legs of diabetics is given. Diabetes exerts some specific toxic effect upon the spinal cord or peripheral nerves dependent primarily upon the abnormal nutrition of inadequately controlled stages of the disease, but favored by the degenerative changes consequent upon advancing years and vascular disease. An increase in the total protein of the cerebrospinal fluid was observed in four cases. Treatment is successful and prognosis is ultimately good. Diabetes should be suspected in cases of obscure pain and paralysis of the legs just as it is in the presence of gangrene, furunculosis, or the classical symptoms of the disease.—J. C. D.

Arteriosclerosis in the young diabetic patient. Shepardson, H. C., Arch. Int. Med. 45: 674. 1930.

A group of 50 diabetic patients who had had the disease for at least five years and who were under 40 years of age was studied to determine the incidence of arteriosclerosis as evidenced by roentgen rays. The pathogenesis of vascular disease occurring so commonly in diabetes was also investigated. The average age of the entire group was 23.4 years, and the average duration of the disease was 6.9 years. Eighteen cases, or 36 per cent, gave roentgenologic evidence of vascular sclerosis. The data obtained in this investigation are summarized in six tables. Neither the severity of the diseases nor the presence of associated pathologic changes, with the possible exception of tuberculosis, can be considered as a pathogenic factor in the development of arteriosclerosis in diabetes. The duration of the disease is important only because the causative factor must act over a reasonable period of time before its effects are manifest. The average values of blood cholesterol found in this group were markedly lower than those heretofore obtained, and, paralleling the reduction of lipemia, the incidence of arteriosclerosis was found to be greatly reduced. The definite lessening of the intensity of the damage resulting from prolonged exposure to diabetes, consequent on the addition of insulin to diabetic therapy, has resulted in a marked lowering of the average blood lipid content. The parallel reduction in the incidence of arteriosclerosis apparently necessitates the assumption that altered fat metabolism is the morbid factor in the development of vascular disease in association with diabetes mellitus.

—Author's Summary.

The increased tolerance of pregnant rabbits for insulin. Smith, G. V. S. and G. A. Marks, Surg. Gynec. Obst. 50: 586. 1930.

Pregnant rabbits in the latter third of their gestation period have a greater tolerance for insulin than do non-pregnant rabbits.—M. O. L.

Anatomical and functional modifications of the pancreas in different sexual states of the female (*Contributo alla conoscenza delle modificazioni anatomiche e funzionali del pancreas in rapporto ad alcuni stati della vita genitale femminile*). Spirito F. Arch. ostet. e ginec. 16: 1030. 1929.

The author made both chemical and histological studies of the insular tissue of the pancreas in pregnancy and following castration. Hogs, dogs, rabbits and guinea pigs furnished the material. Evidence of hyperfunction was found in both states, being greater in the castrates.—R. G. H.

The effect of insulin on pathologic glycogen deposits in diabetes mellitus. Warren, S., Am. J. M. Sc. 179: 482. 1930.

The tissues were stained by Best's carmine stain or Langhans iodine method. The pathologic deposits of glycogen tend to disappear in insulin-treated diabetics. The glycogenic infiltration of the liver cell nuclei, heart, pancreatic duct cells, kidneys, and granules of leukocytes was marked in diabetics. The glycogen content of the skin and voluntary muscle was decreased by diabetes.—E. L.

Cholesterol of the blood of diabetic children. White, Priscilla and Hazel Hunt, New England J. M. 202: 607. 1930.

The study is based on 110 diabetic children. The results are summarized under twelve conclusions. Excess of cholesterol is the exception. Severe acidosis, overnutrition, extreme variations of weight, and possibly excess fat in the diet are associated with an increased cholesterol. Age is a factor. The duration of the disease, glycosuria, blood sugar and complications are not directly correlated with the blood cholesterol. In cases of decreasing severity, the cholesterol value tends to decrease.—J. C. D.

The clinical syndrome of hyperparathyroidism. Barr, D. P. and H. A. Bulger, Am. J. M. Sc. 179: 449. 1930.

From an extensive review of the literature and a study of five cases personally the authors conclude that the symptoms of clinical hyperparathyroidism are similar to those produced by the experimental injection of excessive amounts

of parathormone. They include hypotonia and diminished electrical excitability of muscles, decalcification of bones, hypercalcemia and abnormal excretion of calcium in the urine. In some cases there is nephrolithiasis. Hypophosphatemia has been observed. Hypercalcemia is the most significant clinical sign in the diagnosis of hyperparathyroidism. Although it may be found in few other conditions, its presence usually indicates increased function of the parathyroid glands. Hyperplasia of the parathyroids and clinical evidence of hyperparathyroidism have been found in many cases of generalized bone disease, including rickets, puerperal osteomalacia, multiple myeloma and carcinomatous metastases to bones. The parathyroid changes appear to be secondary to the changes in bone. While in some cases the increased function of the parathyroids may possibly serve a useful function, in other cases it becomes actually harmful by increasing the decalcification of the bones. In generalized osteitis fibrosa cystica (von Recklinhausen's disease) the clinical picture of hyperparathyroidism is most frequently encountered. It may possibly be primary and is unquestionably harmful. In such cases removal of parathyroid tissue has accomplished clinical improvement and apparent arrest of the progress of the bone disease. Determinations of the calcium and phosphate content of the serum should be made in all cases of generalized bone disease not only as a matter of interest, but because of their therapeutic indications.—R. G. H.

**Osteitis fibrosa cystica (Osteomalacia?) with evidence of hyperactivity of parathyroid bodies.** Case. Bauer, W., F. Albright and J. C. Aub, *J. Clin. Investigation*, 8: 229. 1930.

The authors studied calcium, phosphorus and nitrogen on the same patient. They found his negative calcium balance on a low calcium diet was markedly increased over that found in normal controls, the urinary calcium excretion high, and the fecal calcium excretion low. The data regarding the calcium metabolism, like the blood serum, are compared with similar data in a man receiving 100 units of parathyroid extract-Collip a day and are found to be almost identical. The calcium abnormalities were unaffected by the removal of two apparently normal parathyroid glands. Because the pathologic physiology in this case is similar to that in an individual receiving large doses of parathyroid extract-Collip and diametrically opposite to that in a patient with parathyroid tetany, they feel justified in concurring in the diagnosis of hyperparathyroidism. It is suggested that a high phosphorus diet might be more efficacious from a therapeutic standpoint than a high calcium diet in this case.

—R. R. Hannon.

**Experimental chronic hyperparathyroidism in dogs without hypercalcemia.** Bodansky, A. and H. L. Jaffe, *Proc. Soc. Exper. Biol. & Med.* 27: 797. 1930.

In 11 growing dogs experimental hyperparathyroidism was produced by daily injections of parathormone. The first injection raised the serum calcium to 15 or 16 mgm. per cent, later larger doses could be given with only a temporary elevation of serum calcium. When the calcium reserves were allowed to replenish, the injection of parathormone again had the usual effect of hypercalcemia. The authors emphasize that hyperparathyroidism without hypercalcemia may exist in patients. Such a condition can be recognized by a negative calcium balance in the absence of hypercalcemia.—M. O. L.

**Viosterol (irradiated ergosterol) in treatment of parathyroid tetany.** Brougher, J. C., *J. A. M. A.* 94: 471. 1930.

Four patients who developed a parathyroid deficiency after bilateral subtotal lobectomy were relieved of tetany by the administration of cod liver oil and subsequently viosterol. Two of these patients did not develop tetany until pregnancy. A fifth patient who developed tetany after an extensive intestinal resection was benefited by the use of viosterol.—A. M. A.

**The effect of desiccated spleen and splenectomy on serum calcium in normal and parathyroidectomized dogs.** Brougher, J. C., *Am. J. Physiol.* 92: 648. 1930.

Splenectomy in normal and recovered thyro-parathyroidectomized dogs produced a fall in serum calcium. Desiccated spleen caused an elevation in serum calcium in splenectomized animals but not in parathyroidectomized ani-

mals. There seems to be an interrelationship between serum calcium, the spleen and the parathyroids, but it cannot be said that the spleen compensates for the loss of the parathyroids.—Author's Summary.

Concerning the functional test of the pancreatic islets in diabetics (*Über die Funktionsprüfung des Inselorgans bei Diabetikern; Untersuchungen im capillaren und venösen Blut nach Zuckerbelastung und nach Insulinzufuhr*). Depisch, F. and R. Hasenöhr, *Klin. Wehnschr.* 8: 1943. 1929.

In most diabetics the difference between the capillary and venous blood sugar after loading with sugar is less than in normal people. The insulin test with simultaneous determinations of the capillary and venous blood sugar is recommended for the recognition of isolated derangements of counter-regulation in the liver and in the tissues. On the basis of the insulin test there is a distinguishable difference between a hepatic and a peripheral or tissue resistance to insulin.—J. Gagnon.

Osteitis fibrosa cystica (Osteomalacia?) with evidence of hyperactivity of parathyroid bodies. Case. Hannon, R. R., E. Shorr, W. S. McClellan and E. F. DuBois, *J. Clin. Investigation*, 8: 215. 1930.

The report of a case which, from clinical and roentgenological studies, appears to be due to osteitis fibrosa cystica. There is a long clinical history of progressive skeletal deformities with frequent fractures which healed slowly, general rarefaction of the bones with no proliferation and some cyst formation. There had been no improvement from dietary, vitamin D, and ultraviolet therapy. Parathyroid extract seemed to aggravate the condition. Blood calcium was elevated, ranging from 13.4 to 16.5 mgm. per 100 cc. blood. The blood phosphorus was low between 1.1 to 3.3 mgm. per cent and mostly below 2.5 mgm. Calcium required daily to maintain him in calcium equilibrium was 0.7 gm., whereas 0.4 gm. is usually sufficient for a normal individual. Seventy to 90 per cent of the calcium was lost in the urine, which is the reverse of normal, and showed good absorption but poor retention of the calcium. The electrical reactions revealed a marked reduction in excitability of muscle and nerve. The conclusion was that the underlying basis for the osteitis fibrosa cystica in this subject was a hyperactivity of the parathyroid bodies.—R. R. Hannon.

Osteitis fibrosa cystica (Osteomalacia?) with evidence of hyperactivity of parathyroid bodies. Case. McClellan, W. S. and R. R. Hannon, *J. Clin. Investigation*, 8: 249. 1930.

Calcium and phosphorus balances are presented by McClellan and Hannon for the previously reported case, which was observed continuously for 154 days. Distinct improvement in the patient's physical condition occurred during his stay in the hospital. An intake of 1 gm. of calcium was found necessary to keep him in positive calcium balance. The positive balance was increased by increasing the intake. No definite benefit could be ascribed to cod liver oil or quartz lamp therapy. Thyroid and pituitary extracts diminished the amount of calcium retained. The excretion of calcium in the urine was not affected by increased intake of calcium, but was increased as a result of giving thyroid extract. The excretion of calcium in the feces was elevated by increasing the intake, and there is suggestive evidence that it was slightly increased by giving pituitary extracts. The excretion of phosphorus in the urine was not significantly affected by either the intake or glandular therapy. The phosphorus in the feces varied with the intake. A positive phosphorus balance was maintained throughout the entire period of observation even in those periods in which there was definite loss of calcium from the body. The removal of two parathyroid glands caused only slight changes in the levels of serum calcium and phosphorus and no change in the basal metabolic rate.—R. R. Hannon.

Glycogen content in the liver of animals injected with Collip's parathyroid extract (*Sur la teneur du foie en glycogène chez les animaux recevant en injection de l'extrait parathyroïdien de Collip*). Parhon, C. I. and M. Cahane, *Compt. rend. Soc. de biol.* 101: 1179. 1929.

In guinea pigs there is a slight but not constant increase of glycogen in the injected animals.—J. C. D.



The effect of parathyroid extracts upon the blood picture (*Über die Wirkung des Parathyreoideaextraktes auf das Blutbild*). Pellathy, S. v. and J. v. Fernbach, *Endokrinologie*, 3: 406. 1929.

Parathyroid extracts administered subcutaneously increased the number of myeloid cells. The effects seem to be through the nervous system rather than due to blood calcium. The effect is sympathotonic. It should be useful in vagotonic diseases, such as asthma.—B. C.

Tetany associated with arrested growth and striation of bones. Stannus, H. S., *Proc. Roy. Soc. Med.* 23: 69. 1930. (Clin. Sect.)

The patient was a boy 15½ years old who, in January, 1930, after some "upset," began to cry. This was immediately followed by respiratory spasm with contraction of the muscles of the chest and neck. Four days later a second such attack occurred in which the hands were also affected. Since then the spasms have occurred 2 to 3 times each evening. A diagnosis of tetany was made and a spasm was easily induced at will by causing the boy to breathe forcibly for 2 or 3 minutes and could be cut short by an injection of a few drops of a 5 per cent solution of calcium chloride into a vein. Skiographic examination showed some transverse striation at the lower end of the shaft of the tibia. The author remarks that in this case there has been a deficiency of vitamin D in the diet.—I. B.

Morphological contributions to the question of the endocrine function of the epiphysis (*Morphologische Beiträge zur Frage der endokrinen Funktion der Epiphyse*). Brandenburg, E. v., *Endokrinologie*, 4: 81. 1929.

On a basis of 157 human and 82 pig pineals studied, the writer concludes that the work of Aschner is erroneous and that there is no relationship of pineal shape to sex; no relationship of shape to pregnancy; and that there is no relation between the calcium content of the gland and pregnancy—or even sex. —B. C.

The geographic distribution of goiter in Russia (*Über die geographische Verbreitung des Kropfes in Russland*). Arndt, H. S., *Endokrinologie*, 4: 176. 1929.

Goiter distribution in Russia shows that it is not racial, and further studies indicate there is no "racial disposition"; in other words, the causal factor is external to the individual, possibly in the food or water supply which may be short in iodine content. Geological formations are discussed in this relation, but conclusive evidence seems absent.—B. C.

Sympathetic activity after prolonged administration of thyroxin. Blau, N. F. and Helen McNamara, *Proc. Soc. Exper. Biol. & Med.* 27: 997. 1930.

Large cats were made hyperthyroid by treatment with thyroxin for 35 to 57 days. In these and in normal cats under paraldehyde anesthesia, blood pressure tracings were made before and after the intravenous injection of .003 mgm. per kilo of adrenaline chloride. The rise in blood pressure averaged 106 per cent higher in the hyperthyroid cats than in the normal ones.—M. O. L.

Carcinoma of thyroid with metastases. Buxton, J. D., *Proc. Roy. Soc. Med.* 23: 58. 1930. (Sect. Surg.)

This specimen was removed at autopsy from a woman aged 53, who came to the hospital because she had broken her arm. She had a thyroid tumor, which she said had been present for 2 years, and there was a large swelling on the skull which had been there for a year. At the autopsy there were found the large tumor of the skull and two secondary deposits in the jaw; the right humerus was infiltrated with growth, and two pathological fractures were present. There was a secondary deposit in the lower end of one femur. The thyroid was carcinomatous and the involved bones showed carcinoma but no colloid.—I. B.

Some notes of our present knowledge and ignorance of thyroid function. Cameron, A. T., *Canad. M. A. J.* 22: 240. 1930.

A review dealing with the chemistry of the thyroid, the general distribution of iodine, the prophylactic use of iodine, and the pre-operative treatment of thyroid cases with Lugol's solution.—Author's Abst.

Blood volume in hyperthyroidism. Chang, H. S., *Proc. Soc. Exper. Biol. & Med.* 27: 881. 1930.

In 17 cases of exophthalmic goiter and one of toxic adenoma the total blood volume, measured by the CO method, was somewhat increased over the normal. In 14 patients after subtotal thyroidectomies the total blood volume decreased from 7 to 28 per cent. Treatment with Lugol's solution diminished the blood volume along with the drop in basal metabolism.—M. O. L.

The treatment of toxic thyroid with rays of short wave length. Clement, G., *Radiol. Rev. & Chicago M. Rec.* 52: 65. 1930. Abst., *Arch. Physical Therapy*, 11: 142.

Before 1903 the treatment of the toxic thyroid was almost entirely medical. Since 1903 it has been largely surgical. From about 1910 to the present time, radiation, either by x-ray or radium, has been advocated and is slowly but surely gaining ground. Statistics show that about the same number of patients are benefited by radiation as by surgery. Two types of radiation are presented. One case is reported showing what may be accomplished by radiation. The author feels that the patient with toxic thyroid should be given the advantage of radiation therapy, since the treatment causes no pain, no scar, little or no loss of time from hospitalization, no operative mortality, and because the results are as good as by any other method of treatment.

Hyperthyroidism and pregnancy. Clute, H. M. and D. H. Daniels, *Am. J. M. Sc.* 179: 477. 1930.

In the Lahey Clinic, Boston, the incidence of pregnancy in 3,678 cases of hyperthyroidism was 0.41 per cent. From a study of this material it is concluded that special care is needed that the normal elevation of metabolism in late pregnancy is not interpreted as evidence of thyroid disease. Hyperthyroidism does not cause an unnatural termination of the pregnancy in the majority of cases when it is properly treated. It is believed that pregnancy does not increase the toxicity of primary hyperthyroidism except as the increased proplasmic mass of pregnancy brings some increase in metabolism. Pregnancy is, however, distinctly an added burden in hyperthyroidism which should be avoided if possible. Babies born of thyrotoxic mothers are not abnormal. Pregnancy does not appear to be a cause of primary hyperthyroidism. Pregnancy after thyroidectomy for primary hyperthyroidism does not cause recurrence of thyroid toxicity. Babies born of mothers who have had thyroidectomy for hyperthyroidism are normal. Thyroidectomy for primary hyperthyroidism can be undertaken during pregnancy with safety to both mother and child.—R. G. H.

Resistance to thyroxin (Uber Thyroxinresistenz). Falta, W., *Endokrinologie*, 5: 62. 1929.

The author calls attention to the occasional occurrence of very high resistance to thyroxin in human subjects. Two personal cases are cited. The condition is probably to be ascribed to abnormality of the central nervous system. —R. G. H.

Angina pectoris associated with exophthalmic goiter and hyperfunctioning adenomatous goiter. Haines, S. F. and E. J. Kepler, *M. Clin. N. Amer.* 13: 1317. 1930.

This is an interesting discourse on an important clinical combination with 3 illustrated case histories. Cases of angina pectoris complicated by exophthalmic goiter or hyperfunctioning adenomatous goiter show in many instances definite improvement in the angina after thyroidectomy. The prognosis is poor unless the hyperthyroidism is controlled.—I. B.

**Auricular fibrillation in patients with goitre. I. Value of quinidin based on the study of 114 cases.** Hurxthal, L. M., *Am. J. M. Sc.* **179**: 507. 1930.

This report deals with 55 cases of auricular fibrillation which were treated at the Lahey clinic. Previously, the paroxysmal auricular fibrillation was treated with digitalis in 12-18 grain doses. This method of treatment will slow the pulse but will not exert a favorable action on stopping the paroxysms. Quinidin sulphate, three grains after breakfast is given and then six grains every two hours until the pulse is regular or unpleasant symptoms arise. No more than a total of 39 grains should be given. In the selected cases, the quinidin therapy was successful in 88 per cent. When the hyperthyroidism was uncomplicated with cardiovascular disease, this method of treatment was successful in nearly all cases.—E. L.

**Changes in the adrenals after thyroidectomy (Nebennierenveränderungen bei Thyreoidektomie).** Kedrowsky, W. J. and M. L. Birjukoff, *Endokrinologie*, **5**: 116. 1929.

Working with the sheep as experimental animal, the authors noted that thyroidectomy resulted in 70.5 per cent of the cases in extensive morphological changes in the adrenals. These were generally of a degenerative character. They seemed to occur at random in either the cortex or the medulla. No relationship could be determined between time elapsed after operation and severity of adrenal involvement.—R. G. H.

**Hyperthyroidism associated with cardiac disorders.** Lahey, F. H., *Surg. Gynec. Obstet.* **50**: 139. 1930.

Thyroidism in itself does not by its direct action on the heart produce destructive changes in the heart. That frequently associated with cardiac decompensation is atypical and of the apathetic type; this is less striking and more dangerous than thyroidism of the activating type. The possibility of restoration of cardiac capacity after removal of the associated thyroidism is extraordinary. Toxic adenomata are no more apt to cause cardiac failure than is primary hyperthyroidism or exophthalmic goiter.—A. T. C.

**The affinity of haemoglobin for oxygen, expressed by the constant of dissociation k, in certain cases of hyperthyroidism (Sur l'affinité de l'hémoglobine pour l'oxygène expérimentée par la constante de dissociation k dans quelques cas d'hyperthyroïdies).**

**Note on basal metabolism and total oxygen capacity of the blood in normal cases, anemics, and those with hyperthyroidism (Du rapport du métabolisme basal et de la capacité totale en oxygène du sang chez les sujets normaux, les anémiques et les hyperthyroïdiens).** Litarczek, G., H. Aubert and I. Cosmuesco, *Compt. rend. Soc. de biol.* **102**: 157, 159. 1929.

Studies are reported on the relations between the oxygen demands of the tissues and the supply carried in the blood. In anaemias the blood is oxygen poor, while in hyperthyroidism there is increased demand by the tissues, so that in both diseases there is an upset of the oxygen balance of the same kind. Tables and formulae of these relations are given.—J. C. D.

**Effects of thyroidectomy and thyroxinization on the protein balance of the serum (L'influence de la thyroïdectomie et de la thyroxinisation sur l'équilibre protéique du sérum).** Loeper, M., A. LeMaire, A. Lesure and J. Tonnet, *Compt. rend. Soc. de biol.* **101**: 856. 1929.

Thyroidectomy in dogs reduces and thyroxinization increases the amount of serine in the blood of dogs. This is further evidence of a protein controlling action of the thyroid.—J. C. D.

The use of the planimeter for measuring the degree of evolution and functional condition of the thyroid (*Emploi du planimètre pour apprécier l'évolution de la thyroïde et sa valeur fonctionnelle*). Marza, E. and V. Marza, *Compt. rend. Soc. de biol.* 101: 1190. 1929.

By obtaining an actual measure of the area of the follicles and the height of the epithelium, the condition of the thyroid can be accurately recorded.

—J. C. D.

Thyroid extract in treatment of nephrosis. McClendon, S. J., *J. A. M. A.* 94: 1202. 1930. *Abst. A. M. A.*

The three cases of nephrosis reported by McClendon demonstrate the effect of thyroid therapy in the management of the disease. These cases would seem to show that: 1. Dietetic therapy and the treatment of the existing sinus conditions, or other upper respiratory infection, while important and necessary adjuncts in the treatment of nephrosis, are not sufficient in themselves to control the edema and albuminuria. 2. Thyroid extract, in adequate dosage, is an effective therapeutic agent in the management of the true nephrosis.

The sedimentation velocity of erythrocytes in thyrotoxicosis. Mora, J. M. and J. T. Gault, *J. Lab. & Clin. Med.* 23: 586. 1930.

The sedimentation speed of erythrocytes was studied in 30 cases of thyrotoxicosis, by the Merrzenmeier method, before and after thyroidectomy. The rate was increased in all cases before operation. The administration of iodine decreased the speed of sedimentation in 6 out of 11 cases, and increased it in 5 cases. Thyroidectomy was followed by no increased rate in 13 cases, and by a decreased speed in 14 cases. There seemed to be little parallelism between the sedimentation velocity, the basal metabolic rate, and the clinical picture.

—I. B.

The significance of abnormal metabolic features in the management of thyrotoxicosis. Palmer, W. B., *Ann. Int. Med.* 3: 651. 1930.

This report is from the Presbyterian Hospital (N. Y.), where the combined medical and surgical staff decide as to whether the patient shall receive medical or surgical treatment. Basal metabolism determinations are an index of the severity of the thyrotoxicosis, but clinical judgment must also be considered because of discrepancies between the clinical condition and the metabolic rate. Nitrogen equilibrium should be established. This may require 75-100 per cent above the caloric intake as determined by the basal metabolism tests. Every effort should be made to give sufficient food to produce a gain in weight. The laboratory studies (B. M. R., mineral balance, etc.) are of aid but should be interpreted in the light of clinical judgment.—E. L.

Recurring exophthalmic goiter. Pemberton, J. D., *J. A. M. A.* 94: 1483. 1930. *Abst., A. M. A.*

Of the 878 patients with exophthalmic goiter operated on in the Mayo Clinic during the first 11 months of 1929, the author says five died, a mortality of 0.56 per cent. Of the 1,683 patients with exophthalmic goiter operated on in the Mayo Clinic in 1920, 1921 and 1922, 50 (2.9 per cent) had returned up to September 1, 1929, on account of the development of recurrent symptoms that warranted further surgical treatment. On account of this tendency to recurrence in a small percentage of patients with exophthalmic goiter many surgeons, in order to avoid recurrence of hyperthyroidism, have advocated an extremely radical operation, but Pemberton says he has never seen any convincing data submitted to demonstrate that the results of the radical operation are better than those of the conservative resection. A study of the records of 100 consecutive operations on patients with recurrent hyperthyroidism in exophthalmic goiter in whom previous operation on the thyroid gland had been done in the Mayo Clinic revealed that the average interval of time between the primary operation and the onset of recurring symptoms was 5.4 years, and the longest interval 21 years. The average interval between the first and second operation was 6.66 years. Of the 26 patients who had a recurrence within 12 months, in 9 the interval of time was so brief and the onset so indefinite that it was at least suggestive that the patient never had been entirely free from the disease.

Although there was growth of the remnant of tissue preserved at operation, Pemberton avers that the contention that recurrence of the hyperthyroidism of exophthalmic goiter is wholly attributable to inadequate resection of the gland and that its prevention can be accomplished by more radical resection, even to the point of the production of hypothyroidism, cannot be substantiated by the facts. He believes that the removal of from 65 to 85 per cent of the gland is adequate in a large percentage of cases and that the preservation of a postero-mesial portion on each side of the trachea equivalent to from one-sixth to two-thirds of a normal lobe will afford ample protection against injury to the nerves and parathyroid bodies.

**Myxedema during the administration of iodine in exophthalmic goiter.** Thompson, W. O., Phebe K. Thompson, A. G. Brailey and A. C. Cohen, *Am. J. M. Sc.* 179: 733. 1930.

Myxedema was produced in four patients by the administration of iodine after a subtotal thyroidectomy for exophthalmic goiter. The myxedema could be made to disappear by omitting the iodine or by giving thyroid in addition to the iodine.—E. L.

**The range of effective iodine dosage in exophthalmic goiter. III. The effect on basal metabolism of the daily administration of one-quarter drop of compound solution of iodine and of slightly smaller doses, with a summary of results to date.** Thompson, W. O., A. C. Cohen, Phebe K. Thompson, E. G. Thorp and A. G. Brailey, *Arch. Int. Med.* 45: 430. 1930.

During the daily administration of one-fourth drop of compound solution of iodine to 14 unselected hospital patients with exophthalmic goiter, 7 showed a reduction in basal metabolism of from 10 to 26 points, 6 showed no significant change and one showed an increase. During the administration of one-fifth drop daily to 2 hospital patients with the disease, one showed a reduction of 14 points and the other showed no change. In the one-fourth drop series, the basal metabolism was only slightly lower, and in the 2 hospital patients who received 1.5 drop, no lower during the subsequent administration of 30 drops a day, than during the administration of the small doses. Whereas only 50 per cent of the patients showed a reduction in basal metabolism of 10 points or more during the daily administration of one-fourth drop, 65 per cent showed a reduction during the daily administration of one-half drop, and 88 per cent during the daily administration of 1 drop. The administration of one-fourth drop a day caused an average reduction in basal metabolism of only 9 points (from plus 43 to plus 34 per cent) as compared with 14 points (from plus 40 to plus 26 per cent) for one-half drop and 27 points (from plus 36 to plus 19 per cent) for 1 drop. In the 7 patients who responded to one-fourth drop, the maximum reduction in basal metabolism occurred on the average in 5 days. In 1 patient it had started within 24 hours.

In three of the cases observed, the reaction to iodine appeared to be reversible, the administration of one-fourth to one-half a drop of compound solution daily being associated with an increase in the basal metabolism and in the severity of the disease, and the immediate subsequent administration of large doses being associated with a decrease in both factors. Doses as small as one-fourth and one-half drop of compound solution of iodine a day, even when they are too small to cause a reduction in basal metabolism, may sometimes interfere with the effect of much larger doses given immediately afterward. In mild cases of the disease, this phenomenon does not seem to occur. A comparison of the effects of various doses of iodine, therefore, can be made only by giving each dose to untreated patients with the disease. It is also essential to secure a resting level of basal metabolism before iodine is started. In the routine pre-operative treatment of exophthalmic goiter it is desirable to give suddenly an adequate excess of iodine and not to precede this with small doses.

—Authors' Summary.

**Increased metabolism only one factor in the production and maintenance of the hyperglycemia and glycosuria in experimental hyperthyroidism.** Shpiner, L. B., *Am. J. Physiol.* 92: 672. 1930.

Large doses of thyroid extract do not produce a hyperglycemia and glycosuria in normal dogs. However, in a series of six dogs which had the major

portion of their pancreas removed with the factor of safety reduced to a minimum, it was effective in the production of a permanent hyperglycemia and glycosuria (diabetes). The greater hyperpyrexia which accompanies the subcutaneous injection of sodium nucleinate produces a mild hyperglycemia and glycosuria in normal dogs. In a series of four partially pancreatectomized dogs sodium nucleinate did not cause as marked and persistent a hyperglycemia and glycosuria as did thyroid feeding. The results seem to show that the influence of the thyroid is not solely through its effect on basal metabolism, but possibly through some toxic effect of thyroxin exerted on the islet tissue of the pancreas. In this sense (toxic action of the thyroid hormone), one might speak of an antagonism between the pancreas and the thyroid.—Author's Summary.

A histological and biochemical study of pathological thyroid material, with special reference to the effect of Lugol's solution. Wheeler, D., *Canad. M. A. J.* 22: 157. 1930.

The paper gives the results in a series of 126 cases, some two-thirds of which had received treatment with Lugol's solution prior to thyroidectomy. The thyroids were examined immediately. Parts of each gland were examined histologically, and the remainder analyzed for water, fat, nitrogen, and iodine content. The results were critically analyzed both from the viewpoint of clinical diagnosis and from the actual histological appearance. Wheeler finds that the thyroid gland, whatever its type, shows an increased iodine content after the patient has received a course of Lugol's solution. Those which after treatment present a colloid appearance have a high iodine content, and in such colloid glands there seems to be some relation between this iodine content and the amount of iodine administered to the patient. Such relationship does not exist for non-colloid glands. Nor does the same dosage of iodine (as Lugol's solution) appear to have the same effect on the histology of different glands. Glands in cases of toxic adenoma or Graves' disease that have not received the iodine treatment show a relatively low iodine-content, while those of the same group which after treatment retain histologically toxic characteristics show an intermediate value. The iodine content of a toxic gland increases proportionately as the gland approximates to the colloid picture.—A. T. C.

The effect of the daily administration of iodine on the calorogenic action of single intravenous injections of thyroxine. Wilhelmj, C. M. and W. M. Boothby, *Am. J. Physiol.* 92: 568. 1930.

The daily oral administration of iodine for 17 and 22 days before and for 8 days after a single intravenous injection of 10 mgm. of thyroxine (in a dog) did not influence the calorogenic action of thyroxine. Following the injection of thyroxine the basal heat production rose rapidly and reached its maximal height in from 22 to 70 hours; following this there was a progressive decrease in heat production which reached the original basal level in about 190 hours (8 days). In three control experiments in which iodine was not given the extra heat production averaged 300 calories, and in two experiments in which iodine was given the average was 311 calories. The response of the same animal to repeated single injections of 10 mgm. of thyroxine was constant; the average extra heat production in five experiments amounted to 304 calories, and the maximal and minimal values obtained were within  $\pm 8$  per cent of this average. The daily oral administration of iodine (2 cc. of the compound solution of iodine) was without appreciable influence on the basal level of heat production.—Authors' Summary.

Mild mania on recovering from myxedema. Ziegler, L. H., *M. Clin. N. Amer.* 13: 1368. 1930.

The patient was a woman of 58 whose complaints were loss of strength, especially in the legs; nervousness of more than 1 year's duration; loss of 30 pounds in weight, intolerance to heat, and excessive perspiration. The basal metabolism rate was moderately elevated. A diagnosis of exophthalmic goiter was followed by subtotal thyroidectomy, with a report of "hypertrophic parenchymatous thyroid gland." The patient gained weight up to 40 pounds above normal, felt sluggish and unusually sleepy. The basal metabolism rate was —29. Desiccated thyroid was administered. With rising metabolism rate, the patient became very restless, talkative, distractible, rambling in conversation,

and showed flight of ideas. There was no depression. The threshold of excitability was lowered. As the basal metabolism rate approached normal, her normal personality returned. She lost her excess fat and was not depressed except at short intervals just before she became normal when she wept at times and complained of loneliness. The author concludes that in this case, with the patient always talkative and energetic, myxedema served to depress natural tendencies to expression. On releasing her from this depressing influence by elevating the basal metabolism rate, her natural tendencies to activity and talk became exaggerated, and assumed the clinical proportions of mild mania.—I. B.

# ENDOCRINOLOGY

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### NEW CONCEPTS CONCERNING THE PATHOGENESIS OF OBESITY AND THE PROBLEMS OF BASAL METABOLISM\*

DR. HERMANN BERNHARDT

Assistant of The Clinic

Privatdozent of The University of Berlin.

Whoever is interested in the study of obesity will know the standard work of Carl von Noorden on this subject. It was in 1910 that his book upon obesity appeared for the second and last time. The problems of obesity seemed to be settled.

As to the etiology and pathogenesis of obesity von Noorden believed in the important influence of the thyroid and he thought that most of the cases of obesity are due to a hypofunction of this gland. Von Noorden was the first clinician to carry out a strict analysis of the total metabolism of a patient. He partly based his conceptions on the fundamental studies of Magnus-Levy. Von Noorden pointed out that the total daily metabolism of a person can be considered as compounded from three principal factors:

(1) The basal metabolism: By this term is meant the heat-production when the body is at complete rest and at a sufficient time after a meal to escape the stimulative effect of food. As a rule, twelve to fifteen hours must be passed after the last meal, and a rest of 1-1½ hours must be strictly observed before the beginning of the examination. The basal metabolism of the adult is approximately 960 calories per day per square meter of skin surface. The surface area of an individual may be estimated conveniently from the weight and height by means of a formula devised by E. F. and D. Du Bois.

$$A = W^{0.425} \times H^{0.725} \times 71.84.$$

W=weight in kgm.

H=height in cm.

71.84=constant amount (C).

With advancing age there is a slight falling off in metabolism, while in infancy and childhood there is a notable increase.

\*From the First Medical Clinic of The University of Berlin (Charité), (Direktor: Geheimrat Prof. Dr. W. Hls).

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(2) The second factor is the amount of energy necessary for the muscular work during the day. Naturally, this depends on the amount and the kind of muscular work carried out. Van Noorden calculated the amount for a normal man at light work 840 calories daily and he considered from this number 250 calories as the amount corresponding to the real effect of the work done, 590 calories as the amount for the surplus production of heat in the body, as the human body does not work with the positive measurable efficiency of 100 per cent.

(3) The third factor is the surplus production of heat that results as a reaction to the intake of nourishment. This factor is the smallest and von Noorden calculated about 200 calories per day at the ordinary diet. Von Noorden was of the opinion that this surplus production of heat was due to the work that the stomach, the intestine, and the liver had to do shortly after the intake of food. But later investigations, especially by Rubner and his co-workers, showed that this cannot be the first factor. Fat and oil can be taken in rather large amounts without any noticeable increase in the metabolic rate during the next hours. Carbohydrates show some increase but mostly not very marked. Only the proteins are apt to produce an evident increase in metabolism and this increase occurs so soon after the intake of food that a nervous reaction must play the first role. Rubner was the first to study these problems extensively: he called the increase in the metabolic rate "specific dynamic action of food" (*Spezifisch-dynamische Wirkung der Nahrung*).

The addition of these three factors gives the total sum of the daily metabolic rate of a person. It is clear that the whole metabolism will keep its balance in case that the calories of the daily nourishment correspond to the total amount. Should I keep a normal person out of bed with light muscular work and should I give to this person a nourishment only equal to the basal metabolic rate found in this person, the person would show a negative balance of energy and would lose in weight. Naturally the water and salt intake has to be observed very thoroughly during these experiments. This can easily be done by giving only 700 to 800 cc. of fluid and 5 to 7 gm. of salt daily. I have made such experiments in a series of normal persons and I always found a marked loss of weight when I put them on a diet equal only to their own basal metabolic rate. So one can say that the analysis of von Noorden proved to be right in these normal persons.

Von Noorden, however, claimed that this way to find the total amount of the daily heat production by the addition of the three factors mentioned above had to be used under pathological conditions. All three factors are of importance in this regard and must be studied in the different diseases.

The basal metabolism was studied in a large number of cases of nearly all diseases throughout the whole world. An immense literature exists at the present time upon this problem. Marked differences could only be found in cases of disturbances of the thyroid gland. Friedrich

von Müller and Magnus-Levy were the first to point out this important fact. Slight changes of the basal metabolic rate were found under many conditions. I only wish to mention the slight increase in cases of severe anemia, of hypertonia, of diabetes melitus showing acidosis, of leukemia, etc. Naturally all conditions with increased temperature of the body show increased metabolic rate. Decreased basal metabolism was found in all cases of under-nourishment, in cases of pituitary and pluriglandular cachexia, of advanced Addison's disease, and of nephrosis, especially lipid nephrosis. It is impossible for me to cover this question here completely. As to the clinical standpoint the basal metabolism proved to be of interest and of importance rather only in the cases of thyroid disturbances. Hypothyroidism shows marked decrease of the metabolic rate whereas hyperthyroidism is combined with a notable increase. These facts are of leading importance as to the diagnostic work.

It is very interesting to state that the patients with obesity show in about 66 per cent a basal metabolic rate within the normal limits. In about 25 per cent one even finds a high rate and only in about 10 per cent of the cases a more or less marked decrease could be noted. These numbers are based on my own investigations carried out on more than 100 subjects of obesity of all kinds. The fact that obese people show, as a rule, a normal basal metabolism has also been stated by other investigators. I mention A. Loewy, Hausleiter, Kestner, and his assistants, Grafe, Lauter, Strouse, Wang, Means, Minnig, McCaskey and Eidelsberger.

As to the second factor, the surplus energy due to the muscular work, I wish to mention the investigations that H. Gessler (Heidelberg, Germany), published some years ago. He studied the heat production of normal and of obese people doing the same muscular work and found a rather marked difference, obese people showing 20 per cent less increase during the work than normal people. Unfortunately, other investigators (S. Lauter, S. Strouse) and myself could not confirm these results. Obese people show, as a rule, the same increase of metabolic rate during muscular work as normal people. On the contrary, when forced to heavy work they show a higher increase and mostly a longer lasting increase than normal people as S. Lauter and myself could state. As to the period following muscular work, I shall speak about this later on more extensively.

The third factor, the specific dynamic action of food, especially of proteins, has been studied in obese people by many authors. Jaquet and Svenson were the first to state that there is mostly a marked difference between healthy people and obese persons, the specific dynamic action of food being smaller in the obese. Many authors could establish this fact: G. von Bergmann, Staehelin, Rolly, Kestner, Plaut, Liebesny, Knipping, Dürr, Biedl, Strouse, and so on. My own investigations showed the same, but it must be stated that sometimes also a normal specific dynamic action can be found, especially in cases that offer symptoms of hypofunction of the gonads. But even if one would suppose this third factor

being only one-fourth of the normal it would not be possible to base the pathogenesis of obesity on that point alone.

The work I have carried out on obesity since 1923 showed that the critical point lies indeed in another line. I desired to study the importance of the basal metabolic rate found in obese people. I did it by keeping the obese for three to four weeks and longer on a diet that was in its calorie amount equal to the amount of the basal metabolism of these patients. I laid stress on the fact that these patients performed light muscular work, mostly by walking around for a certain time during the day. I am of the opinion that we do not deal with normal and comparable conditions if we would keep our patients submitted to these experiments in bed for all twenty-four hours of the day. The light muscular work that all normal people carry out every day plays such an important role in the balance of the daily metabolism that we get other than normal conditions when we omit this factor totally. I wish to quote the old German proverb: "Das Bett zehrt", which means, lying in bed for a long time without any muscular exercise one will lose very soon in weight and strength. It is obvious that the factor of inactivity plays a large role in this condition.

The patients who were held on that strict diet equal to their own basal metabolic rate were kept under rigorous observation. The fluid intake was restricted to 700 to 800 cc. and the amount of salt did not exceed 7 gm. daily so that there was no possibility of retention of water or salt. It was very interesting to state that nevertheless nearly all patients that showed endogenous obesity did not lose in weight during this diet. Some of them even gained weight noticeably. These experiments were repeated with the utmost accuracy and today I can state with absolute conviction that most of the patients with endogenous obesity, if held on a diet equal to their own basal metabolic rate, even for weeks, will not lose in weight but may sometimes even gain in weight during this period.

These results made evident the fact that in these obese people the analysis of metabolism given by Von Noorden did not hold, for if it would prove correct, the obese patients should show marked loss of weight during this strict diet. On the other hand, S. Lauter and myself have found that during muscular work the metabolic rate increases in about the same amount in obese as in normal persons. The results of these two investigations seem to be in sharp contrast. After repeated attempts I succeeded in analyzing the whole problem. I could state by taking the metabolic rate of these patients with only very short intervals during the whole day that there are periods where the metabolic rate is markedly less than that taken in the morning. I call these periods of decreased metabolic rate "negative phases" (negative Phasen). They occur most noticeably in the time following light muscular work but also very often after the intake of food. In this case you will find at first a short period of slight increase of the metabolic rate followed later on by

a longer period of marked decrease. These negative phases also occur during sleep (Talbot's case). It is very important to state that all the negative phases as a rule, last longer than one or two hours so that the caloric effect is very important. If one estimates on one side all the positive phases of metabolism and on the other side all the negative phases in obese persons for twenty-four hours, one very often comes to the result that the negative phases are so marked that they balance the positive ones. In this way a total sum of the daily heat-production results that is very near to the basal metabolic rate, in some cases it is even smaller than this amount. One gets an idea of the results more clearly when one draws a curve according to the series of findings during twenty-four hours. The basal metabolic rate is taken as the horizontal axis so that the positive phases are above the line and the negative phases beneath. It is very easy to get the balance of the positive and negative sums by a mathematical formula. Also simple geometrical comparison is possible.

That there are obese people who keep their weight under a very strict diet taken even for a long time has been observed by many authors before me, but it was only a mere statement of facts. No analysis was given. Von Noorden himself reports in his book some of these cases. Very interesting is his report of a man aged thirty-nine years, who weighed 102 kgm. This man was kept for three months on a diet of 1720 calories or less and though he exercised daily in the open air he did not lose more than 1 kgm. weight. Von Noorden estimates his actual caloric requirements at about 2700 calories daily. A control subject weighing 98 kgm. exercising less actively lost nearly 5 kgm. in four weeks on the same diet. Schwenkenbecher, Salomon, A. Loewy and F. Hirschfeld, Grafe, Ueber, Düring, Talbot, Plant and Strouse reported similar cases. The conclusions, if drawn, varied. Strouse, for instance, stated that persons showing the predisposition of so-called constitutional obesity show no interdependence between food intake, energy expense and weight. Dietary studies proved that certain types of obese persons maintain their weight without regard to the usually accepted caloric balance. In a second paper he comes to the conclusion that neither excessive underweight nor excessive overweight is associated with a constant change in basal metabolism. "Obesity cannot be caused by changes in the basal metabolism."

Out of my own observations I wish to mention a patient of thirty-four years of age, 156 cm. in height, and 83 kgm. in weight. As this patient was very eager to lose weight she remained under strict observation for a long period. Her basal metabolic rate was taken nearly every day and proved to be very constant: 1750 calories. Her diet was fixed at this amount. During an observation of three months this patient gained 1.5 kgm. It was very interesting to observe that the weight showed a relation to the menstruation. The highest weight was always found just before the beginning of the menstruation. Besides this she complained of severe headache during the week before the period. During menstruation the headaches disappeared and a slight decrease of weight was observed. It is

important to say that the patient was always held at 800 cc. of fluid and at less than 7 gm. of salt daily. Later on her diet was restricted to a milk diet of Karrel (800 cc. of milk). This is equal to about 600 calories. Under this diet the patient showed loss of weight, about 0.8 to 1 kgm. a week. The analysis of metabolism in this patient proved that she showed very long but not very deep negative phases and that the daily metabolic rate had to be considered as smaller than the basal metabolic rate taken in the morning.

The factor of the negative phases, especially after light muscular work, is also apt to elucidate those cases of obesity, where keeping at rest proved more efficient as to the loss of weight, than light muscular work. G. Leven, in 1904, reported the history of a patient of 108 kgm. who had sold his car and walked to his office every morning in order to lose in weight. But he did not lose at all, although his diet was very strict. However, Leven succeeded in having him lose some weight by applying a rest therapy to him without changing his diet.

Normal persons, as a rule, show no negative phases during the day, but there is no doubt that by and by more conditions of that kind will be found and that there are transitions from obese people to the normals. One can prove it by the fact that one can hold a normal person at the same condition as to the muscular work and can alter the nourishment to a rather large amount without a change of weight. Grafe and Koch demonstrated this extensively.

It is very interesting, as I determined, that also in normal persons these negative phases occur when there are conditions that require highest economy of energy. A very good example is the analysis of the metabolism of convalescents who make a rapid gain in weight. They show, as a rule, a perfectly normal, even a high basal metabolic rate, but show after light muscular work marked negative phases. Mostly these phases are shown also after the intake of food. It will be very important to study the different diseases as regards this problem of the relation of the basal metabolic rate to the whole heat-production during twenty-four hours. It is clear that our view and idea about the basal metabolic rate must be altered, and that the term "basal metabolism" is no longer to be regarded as apposite. This term is a translation of the German expression, "Grundumsatz," that was introduced by A. Magnus-Levy. This metabolic rate can no longer be considered as characteristic of the whole day's metabolism. In German I have suggested the simple descriptive term, "*Ruhe-nüchternumsatz*," and in English I would say, "*standard metabolism*" (Krogh, E. F. DuBois).

As to the clinical aspect of obesity the studies made during the last twenty years are closely connected with the investigations of endocrinology. Soon after it was stated that the function of almost all endocrine glands is important for certain processes of metabolism, the problem of obesity as an endocrine disturbance was started. It is very interesting to follow this development. Nowadays we can say that there is no endocrine gland that was not accused by some authors of being the cause of obesity.

A gross discrepancy arose and the clinic tried to get its best out of the different theories.

As to the routine procedure the history of the patients mostly gives the best help, especially as to the question whether we deal with exogenous obesity caused by overeating and inactivity or with an endogenous obesity. Besides this, the physical examination with special reference to endocrine signs, fat distribution, hair, teeth, skin, sex organs, measurements, etc., is important. X-ray pictures of the sella turcica, sugar tolerance skiagrams of the thymus region, basal metabolic and blood chemistry studies are added. The cases of endogenous or endocrinopathic obesity are divided according to the endocrine symptoms found mostly along the following division:

- (1) Pituitary disease (Froehlich's disease, dystrophia adiposo-genitalis) as evidenced by girdle obesity, small sella turcica, delayed menses or amenorrhea, deficient sex organs, disturbances of the water and salt metabolism.

- (2) Thyroid disease, present or absent struma, low basal metabolism, slow pulse rate, myxedematous infiltration, etc.

- (3) Thymic origin: type, low blood pressure, vagotonia, positive thymus shadow.

- (4) Pre-diabetic type.

- (5) Gonadal type: trochanteric obesity, menopause.

- (6) Mixed type: pluriglandular type.

- (7) Very seldom pineal origin, adrenal origin, and pancreatic origin.

Besides this there is a group of unexplained endogenous obesities that is mostly called idiopathic obesity where no special endocrine symptoms are found. Lipomatosis and Dercum's disease may be left aside as they show so many symptoms that lie outside the realm of obesity.

This clinical division is used in nearly all clinics of the United States as I found by observation and from the voluminous literature.

I cannot deal extensively with the different factors of routine procedure in obesity. However, I wish to mention that we should lay more stress on the respiratory quotient: the ratio  $\text{CO}_2:\text{O}_2$ . If this quotient shows a high value, near 1.0 or even over 1.0, we deal with a case of obesity that presents a marked tendency to saving his fat tissues and to synthesizing carbohydrates to form fat. Most of the patients with pituitary or cerebral obesity offer this phenomenon. Clinically, it is of importance as it indicates that it will be very difficult to get these patients to use their own fat tissues. Especially when a normal or high metabolic rate is found the difficulty of producing fat decomposition is rather insurmountable. On the other hand, a low respiratory quotient gives a good clinical prognosis as the fat decomposition is preferred. During the period of losing weight all obese show normal or low respiratory quotients.

That the water- and salt-metabolism must be observed in all cases of obesity is a well-known fact. This factor can be so important that it outdoes all others and that one gets no therapeutic results before taking account of it. But on the other hand, it must be stated that the theory that there is always a hydrophile factor in obesity and that the fat tissues contain more water than normal tissues does not hold. I only mention Foster and Benninghoven, who found that the fat tissues of their rats brought experimentally to marked obesity, was very poor in water and that the fat rats as a whole showed much less water in their body than the control animals. It is a well-known fact that the specific weight of fat people is lower than that of normal persons.

Many of the patients with pituitary or cerebral obesity show marked signs of increased cerebral pressure: headache, slow pulse rate, tendency to vomit, nausea, subfebrile temperatures, tendency to retain water and salt, and a high metabolic rate in the morning. If one does a spinal puncture the spinal pressure is found increased. One is forced mostly to let ooze out about 40 to 60 cc. until the pressure becomes normal. This procedure lowers the cerebral pressure for some time; in rare cases we get even a lasting effect. Most of the complaints disappear shortly after the puncture. It is very interesting that the puncture produces marked change in many regards. The basal metabolism rate shows a notable decrease, the temperature comes to normal and the disturbances as to the water metabolism are no longer found. These three phenomena are not combined physiologically. We find the change of the metabolic rate also in patients who do not show any change as to the temperature as there was no rise in temperature at all.

The high metabolic rate of these patients with cerebral obesity offers many other interesting features. It is possible to lower it by average or high doses of preparations of the anterior lobe of the pituitary gland, or by very small doses of thyroid preparations. It is interesting that as a rule the respiratory quotient also comes down to a normal rate by these modifications.

Surveying the whole literature of obesity, especially since 1900, and adding the new investigations of my own, one must come to the conclusion that the ideas we have had until now upon the pathogenesis of obesity are not apt to explain all the different facts involved. It is impossible to consider a certain endocrine gland as the cause of obesity. Many of them may be of importance. However, never the endocrine gland alone gives the decision, for we see the same disturbances of the gland without an obesity resulting. Hypothyroidism is found very often without obesity and so are hypogenitalism and hyperpancreatism, and so on.

The regulation of the weight of man is quite the same as the regulation of temperature. The most important factor is the function of the regulative center in the central nervous system. This center is located at the base of the brain in the hypothalamus somewhat behind the tuber cinereum. This region is very near to the pituitary body and it is diffi-

cult to explain the role of this gland. As things are up to date I think it is best not to try to separate the role of the hypophysis from that of the hypothalamic centers. About eight years ago Biedl, one of the best known endocrinologists of the world, pointed out that the hypophysis functionally forms a physiological unity with these centers and I think that even now we cannot give a better explanation. Nevertheless, the analysis must be studied further. On the other hand, I am of the opinion that as to the clinical standpoint it does not make much difference whether we apply a treatment to the pituitary body itself or to the region near by.

The regulation of the body weight is a very complex problem. Many lesions and changes in the different organs are apt to bring out a tendency for gaining weight, but the weight will change only if the central regulation fails. The clinic shows this every day. If you extirpate the ovaries of ten women not all ten will develop obesity, only four or five. Very often the central regulation succeeds in keeping the old weight even under such a disturbance of the endocrine balance suddenly applied. The small appetite of the myxedematous patients is one of these regulative signs to keep the weight.

But in case the central regulation fails the weight will change. This failing can occur in a quite healthy central regulation, when the demands given to it by the different changes are too strong. Very often the central regulation itself is not all right, maybe there is a weakness of primary origin or that secondary disturbances occur. It is very interesting that during the last twenty years from all countries of the world such cases of central nervous disturbances leading to severe obesity have been published: I mean the obesity after encephalitis, the so-called post-encephalitic obesity. Here we deal with very clear conditions as histological demonstration is possible. The same effect of circumscribed lesion of the central nervous system is given in cases of tumor of the brain and of softening of the brain occurring in arteriosclerotic processes.

From the standpoint of the views and ideas given here the whole problem of body weight can be explained, overweight and underweight being included. Also partial obesity can be discussed in this line, the big nervous factor in these cases has been stated very often. I wish to mention only two points as to partial obesity. I think there is enough proof to state that the different endocrine glands do not influence the subcutaneous tissues of the whole body in the same measure. The thyroid, for instance, is more active in the upper parts of the body, whereas the region of the girdle, hips and the lower extremities yield more to the endocrine secretion of the gonads. Many women after castration or after the menopause show marked increase of fat at the hips but decrease of fat in the upper parts of the body. In Basedow's disease we are accustomed to see meagerness, especially in the upper part of the body. I think that this phenomenon is a remnant of the original metameric structure of our body.

The problem of partial obesity has also to deal with the theories of primary lipogenic tendency of the peripheral tissues. These theories were



started by F. Kraus and G. v. Bergmann in Germany. But even if one agrees with these theories the central regulation will play its role. Only in case that this center fails to bring forth the reactions necessary to avoid such a local process, partial obesity will be possible.

The view of the predominant factor of the central regulation as regards the body weight is well supported by a series of experimental findings. I only mention the names of the authors as it is impossible to go into details: Asehner, Bailey and Bremer, P. E. Smith, Foster, Benninghoven, Raab, Grafe, and Grünthal.

The standpoint brought out is of high importance for the clinical work. Three points may be discussed:

(1) It is no more possible to base the total daily metabolic rate of obese people on the amount of the so-called basal metabolism by adding certain amounts as to the reaction of intake of food and of the muscular work carried out during the day. The role of the "negative phases" must be considered; it is possible that these negative phases balance the positive phases during the day.

(2) When we assemble the different symptoms and findings presented by an obese patient, we must not try to consider them all as simple signs of the disease. Some of them may be the expression of reactions of the body to the obesity developed. One of these symptoms, that surely plays the role of a reaction, is the normal or high metabolic rate that many obese show in the morning.

(3) It is very important to look for symptoms that indicate a disturbance of the central regulation: signs of increased cerebral pressure, lethargy, or nervous symptoms. A very accurate history must be taken as to these symptoms.

(4) It is necessary to give a new classification of the different kinds of obesity. The division into exogenous and endogenous obesity now prevailing must be discontinued. Most of the cases are mixed as to this regard. I include in my scheme also the pure exogenous cases. It is true that these people are not really sick and do not offer any organic disturbances, but the physiological problem is the same. The normal organism and the normal central regulation can stand only a certain amount of overeating. The limit is very different for individual people. It is one of the most important factors of the so-called constitution or condition of the body. The most important factors may be shortly mentioned:

- (a) The resistance of the body against changes of the pH.
- (b) The resistance of the body against changes in weight.
- (c) The resistance of the body against changes in temperature.
- (d) The resistance of the body against infection.

In all these fundamental things the nervous system is highly involved and I think that under the view of phylogenesis these functions are the

foremost and oldest of the nervous system. The location of the different centers concerned reveals the same as they are all situated in the phylogenetically oldest parts of the central nervous system.

The following is the classification of obesity that results from my investigations:

- I. Obesity as the result of primary disturbances of the central regulation of metabolism.
  - A. Purely cerebral disturbance (encephalitis, tumor, etc.)
  - B. Purely pituitary disturbance.
  - C. Mixed forms.
- II. Obesity as the result of secondary functional disturbance of the central regulation of metabolism, as primary disturbances may act:
  - A. Endogenous factors:
    - (1) Disturbances of general behavior (such as of hunger, thirst, and activity).
    - (2) Disturbances of the endocrine glands:
      - (a) Single glands: thyroid, gonads, adrenals (especially cortex), pancreas, pineal.
      - (b) Pluriglandular disturbances.
    - (3) Disturbances of the periphery (primary lipogenic tendency of the tissues according to theories of Fr. Kraus, and G. v. Bergmann).
  - B. Exogenous factors:
    - (1) Overeating.
    - (2) Muscular inactivity.
    - (3) Mixed forms.

As to the therapy of obesity I wish to mention the following points:

- (1) It is best to take the metabolic rate in every case of obesity. If we deal with an adult person and no complications are present, especially no disease of the circulatory system and of the kidneys, and of the liver, it is indicated to give a diet that is equal only to the amount of the metabolic rate in the morning (standard metabolism). The patients may have slight muscular exercise every day. As to the diet, 0.8 to 1.0 gm. of proteins for every kilogram of the calculated normal weight of the patient is sufficient to avoid disturbances of the nitrogen metabolism. Even under a very strict diet this amount must never be decreased markedly. The rest of the calories are divided among carbohydrates and fat in such proportion that the ketogenic-antiketogenic ratio is about 1.5 to 1, but should not exceed this amount. This would be the highest ratio of fatty acids and

glucose without ketonuria as was shown by R. T. Woodyatt and others. Woodyatt's formula is in this case:

Fat (in gm.) =  $2 \times \text{Carbohydrates (in gm.)} + \frac{1}{2} \times \text{Proteins (in gm.)}$ . Hence, a diet of

50 gm. of proteins.

40 gm. of carbohydrates.

105 gm. of fat.

would show the ketogenic-antiketogenic ratio of 1.5 to 1. Also the formulae of P. A. Shaffer, of R. S. Hubbard and F. R. Wright and of R. M. Wilder and M. D. Winter may be used. Very often it is advisable to begin with a diet that shows a ketogenic-antiketogenic ratio of 1.0 to 1.0.

If it appears necessary to restrict the diet even more and to go below the number of calories equal to the standard metabolic rate of the patient, it should be done by reducing the amount of the fat, keeping proteins and carbohydrates on the previous level. However, this whole dietary procedure does not apply to every case as sometimes individual factors interfere with its routine application. It is advisable to keep the patients under strict observation long enough to make sure that they agree with the diet. Vitamines and Calcium must be considered in the diet. Fluid intake must not exceed 800 to 1000 cc. a day; salt not over 7 to 8 gm. per day. It is striking what effects are obtained by such a dietary procedure. Similar good results were reported recently by F. A. Evans and J. Strang (Pittsburgh).

(2) Light muscular work, as a rule, does not cause any noticeable effect as to loss of weight. On the contrary, rest therapy sometimes produces better results. Heavy work naturally is effective, but it is mostly not without danger as to secondary disturbances, especially of the circulatory system.

(3) If it is not possible to give such a strict diet, good preparation of the anterior lobe of the pituitary gland is advisable. Rather high doses must be given. I obtained very good results with the German preparation, "Praephyson," in doses of 3 to 8 tablets a day or 1 cc. subcutaneously. It is indicated to add very small amounts of thyroid preparations, a half to one tablet a day or every second day. High doses of thyroid are very dangerous and must never be used. Ovarian preparations are mostly without any effect on obesity.

(4) A cautious protein therapy may be tried and is often a good adjuvant.

(5) Careful roentgen treatment and diathermy of the pituitary body and the adjacent parts of the brain have been started in many clinics. They seem to be of value in some cases, but it is impossible to draw definite conclusions from the small number of observations.

(6) The loss of weight must never be too fast in order to avoid secondary disturbances.

The principal point of this paper is to give a new aspect to the problem of obesity as a problem of caloric balance. There is no proof until now that the laws of caloric balance do not hold in obesity. In this regard my work is in line with the investigations that Newburgh and his associates published recently.

As to the technic of my investigations I wish to add some remarks about the basal metabolic rate, "*standard metabolism*." Nearly all investigators agree that it is necessary to take the metabolic rate not before twelve to fifteen hours after the last intake of food. As to the muscular work there occur many differences in the technic. In many institutes complete rest of from twenty to thirty minutes is considered sufficient for taking the basal metabolic rate, others require a rest of one hour or more. My investigations show that the influence of muscular work on the metabolic rate can be very marked for a long time. It is important to state that the metabolic rate determined shortly following muscular work may be either higher or lower than the real metabolic rate in the morning at complete rest. If one wishes to get absolutely exact and constant amounts for the basal metabolic rate it is not only necessary to take the rate twelve to fifteen hours after the last intake of food, but also to observe complete rest during these hours. These conditions can only be fulfilled under hospital treatment, where the patients are brought to the apparatus in their beds or the apparatus transferred to them. If there was only slight muscular work carried out, for instance, a walk of not more than half a mile, a rest of three to four hours would be sufficient to free the body of the influence of the muscular work.

The big difficulties involved in the technic and theory of the basal metabolism have been pointed out by Benedict (1915). Everyone dealing with these things should read it. In this paper Benedict showed that there are conditions under which the metabolic rate sinks during sleep at night markedly below the level of the so-called basal metabolism taken in the morning at complete rest. This is one of the best examples of negative phases. And to be sure the negative phases during sleep play a role in certain cases of endogenous obesity and are an important factor in my criticism of the basal metabolism as a basis for the calculation of the total twenty-four hour metabolism. These facts with others lead to the conviction that the "basal metabolism" is not at all the "minimum metabolism" of a person as many authors maintain. Besides this, many investigations have shown that the amount of the so-called basal metabolism may be markedly altered very often by factors that obviously have no, or nearly no, influence on the amount of the total metabolic rate of 24 hours (Benedict, Arnoldi, my own investigations). In practical daily routine work it is completely impossible to eliminate all these factors.

To better illustrate my contentions some curves are offered that show the negative phases occurring in obese people after slight muscular exercise consisting of flexing each leg eight times a minute, while lying down. Figure 1 gives the curves of two patients:

Patient N. (thirty-nine years of age, 176 cm. tall, and 102.0 kgm. in weight), who showed a typical case of overeating; his weight could be easily reduced by slight dieting. It is interesting to see that he did not offer any negative phase after muscular work. The other subject, Patient

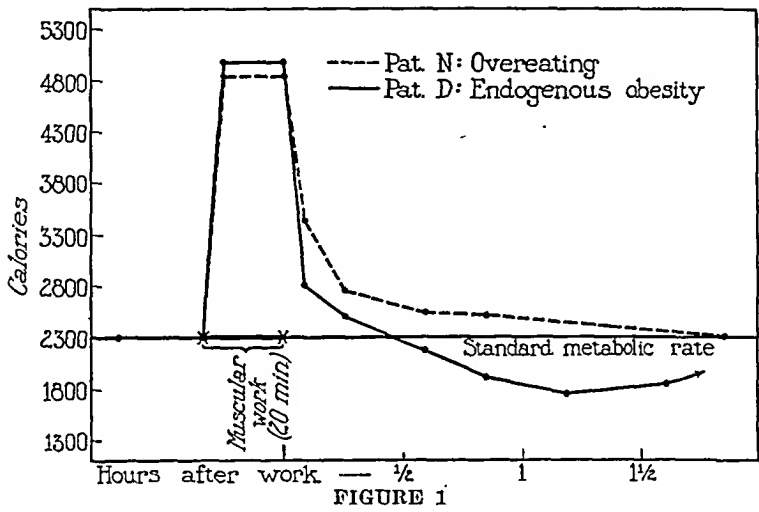


FIGURE 1

D. (forty-nine years of age, 168 cm. tall, and 103.0 kgm. in weight), showed a typical case of endogenous, so-called cerebral obesity. It was very difficult to influence his weight as it yielded only to a very strict diet. The basal metabolic rate of the two patients was almost identical, a fact that permits good comparison. Patient D. showed a rather marked negative phase after muscular work.

Figure 2 gives an idea of the extent that negative phases may reach in the patients with endogenous obesity, especially in cases with a high

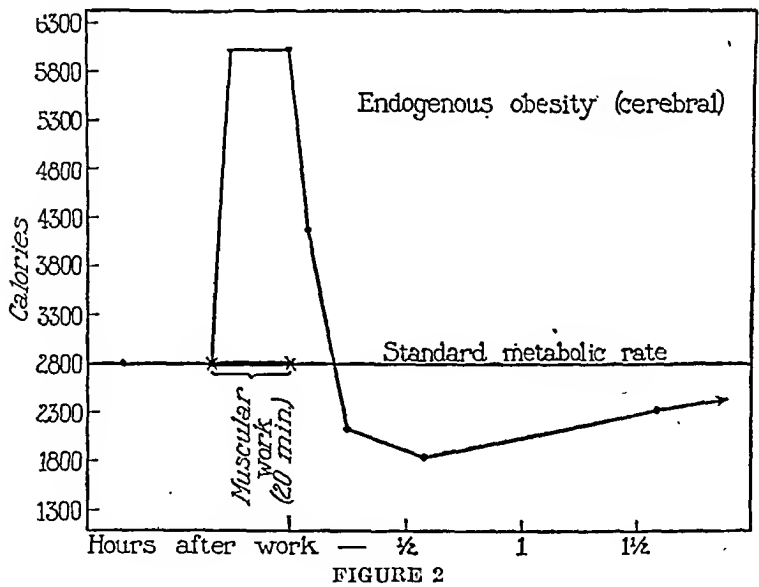


FIGURE 2

metabolic rate in the morning ("standard metabolism"). This is a curve of Patient P1. (fifty-one years of age, 187 cm. tall, and 138.5 kgm. in

weight), who showed a typical endogenous obesity of cerebral character. His standard metabolism was carefully observed and always proved to be rather high (2848.5 calories).

In both figures the standard metabolic rate (basal metabolism) is taken as the horizontal axis, so that the positive phases are above the axis, the negative phases below. The areas bounded by the axis and by the curve give an exact picture of the caloric amounts on the positive and negative sides so that a simple geometrical comparison gives the balance. All the metabolic amounts are calculated for twenty-four hours and therefore direct comparison is possible.

Whoever is interested in the problems brought out here may read my compiled paper on the subject (Bernhardt, 1929). A review of the literature is also given.

#### SUMMARY

(1) The method of calculating the total daily metabolic amount in a person by adding three factors, (a) basal metabolic rate (standard metabolism), (b) caloric amount necessary for the muscular exercise during twenty-four hours, and (c) caloric amount due to the reaction to the intake of food (specific dynamic action of food), was introduced by von Noorden and Magnus-Levy, about thirty years ago. It was believed to be applicable to obese as well as normal people. The studies pointed out in this paper prove that this method does not hold in many cases of obesity, especially that of endogenous obesity.

(2) It was shown that many obese people do not lose weight on a diet calorically equal to their own basal metabolic rate as ordinarily determined, even when given for many weeks. Water and salt metabolism was always carefully taken account of in all of these experiments.

(3) It was demonstrated that there are periods during the day when the metabolic rate sinks markedly under that determined in the morning. These periods of decreased metabolism are found especially during the time of gaining weight. They are evident more after light muscular work than after the intake of food and they occur very often during sleep. I call these periods "negative phases." They can be found in such a degree that they form a complete balance against the positive phases occurring during twenty-four hours so that the whole metabolism rate of the day may show about the same amount as the so-called basal metabolic rate of these patients. The negative phases are seldom found during the time of loss of weight.

(4) It is very interesting to state that negative phases may also occur in normal people under certain conditions. Convalescents from severe diseases during the state of rapid gain in weight are the best examples.

(5) These investigations may give an explanation for the cases described in literature in which obese people did not lose under a very strict diet (Grafe, A. Loewy, Hausleiter, S. Stronse, von Noorden, and others).

(6) As to the etiology of obesity, my experiences lead to a standpoint different from that generally accepted. It is impossible to accuse a particular endocrine gland of being the cause of obesity; disturbances of the endocrine glands are often involved but they do not play the first role. The decisive factor is the function of the hypothalamic regulative center. The regulation of weight closely resembles the regulation of body temperature. The center can be disturbed directly, as for instance in encephalitis or tumor of the brain, or it can fail when the demands directed on it by peripheral disturbances (disturbances of endocrine glands, changes in the peripheral tissues, changes in general behavior, such as hunger, thirst, et cetera), are too great. These new conceptions involve the whole problem of weight, both overweight and underweight.

(7) My experience also leads to the conviction that we must change our opinion about the metabolic rate taken in the morning at complete rest at sufficient time after the last muscular work and twelve to fifteen hours after the last intake of food. The term "basal metabolism" is no more advisable. It would be better to use the term "standard metabolism" (A. Krogh and E. F. Du Bois). The problems of the so-called "basal metabolism" are very complex and are partly discussed in this paper.

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# THE EFFECT OF INSULIN UPON THE RATE OF DIALYSIS OF DIABETIC BLOOD SUGAR\*

ISRAEL S. KLEINER

With the Assistance of

HAROLD BIRNKRANT

AND

THEODORE ROTHMAN

From the Department of Physiological Chemistry of the New York Homeopathic  
Medical College and Flower Hospital.

NEW YORK

and

The Biological Laboratory.

COLD SPRING HARBOR, L. I.

In 1918 one of us (1) compared the rate of dialysis of the blood sugar of diabetic dogs' blood with that of glucose, which had been added to the blood of normal animals. The diabetic blood sugar dialyzed at an irregular rate. The curve usually indicated a delay or even a complete cessation of dialysis during one or more periods, whereas the control dialysis proceeded in a regular, uninterrupted manner.

Although various explanations were offered, the one which appeared most tenable was that part of the blood sugar in diabetes is present in combined form and part free. If the former dialyzed slowly and the latter rapidly and if the combined sugar, after most of the free sugar had dialyzed out, was convertible into free glucose, curves of the type obtained would be possible. We have been engaging in various investigations in the attempt to throw more light upon this phenomenon. One of the first questions which arose was whether insulin would affect this peculiar diabetic dialysis curve. The present note deals with that question.

Since our findings are uniform we need only give two typical experiments, although we have other similar results. One of these is of special interest because it was one of a series in which we used a certain diabetic animal (Dog No. 3), which for a long time apparently gave "normal" curves. This fact was quite perplexing and delayed our investigations until it was finally discovered that, in this particular animal, the period of inhibited dialysis usually occurred quite late, instead of during the first two hours. We have no explanation for this unusual result.

*Methods.* The same general methods, described in the earlier paper were employed. Twenty to fifty cubic centimeters of hirudinized blood were divided in two portions, and each was placed in an animal parchment dialysis bag. Dry insulin<sup>1</sup> (from 1 to about 150 units) was added to one

\*Aided by a grant from the Elizabeth Thompson Science Fund.

<sup>1</sup>We are indebted to Eli Lilly and Company for this preparation. It was labelled "approximately 20 units per milligram," but, as it had been prepared about two years before it was sent to us, it had deteriorated slightly. It was, however, exceedingly potent.

portion; it was then mixed thoroughly to insure solution of the insulin. The other portion had no insulin added. Each was now immersed in 500 cc. or 1000 cc. of Ringer's solution containing glucose (usually 0.15%). In some of the first experiments with the blood of Dog No. 3, novirudin and medicinal insulin solution (Lilly) (from 8 to 12 units) were employed instead of hirudin and dry insulin, respectively. Samples were taken before dialysis, and at intervals during its course. At each sampling, the dialysis bag was removed from the bath to permit of proper mixing and sampling of the blood. Sugar was determined by Myers and Bailey's modification of the Lewis-Benedict method.

*Results.*<sup>2</sup> Curves I and II in Figure 1 show the results of one of the experiments upon the animal mentioned above. Both dialyses proceeded regularly until the sixth hour, at which time, dialysis apparently

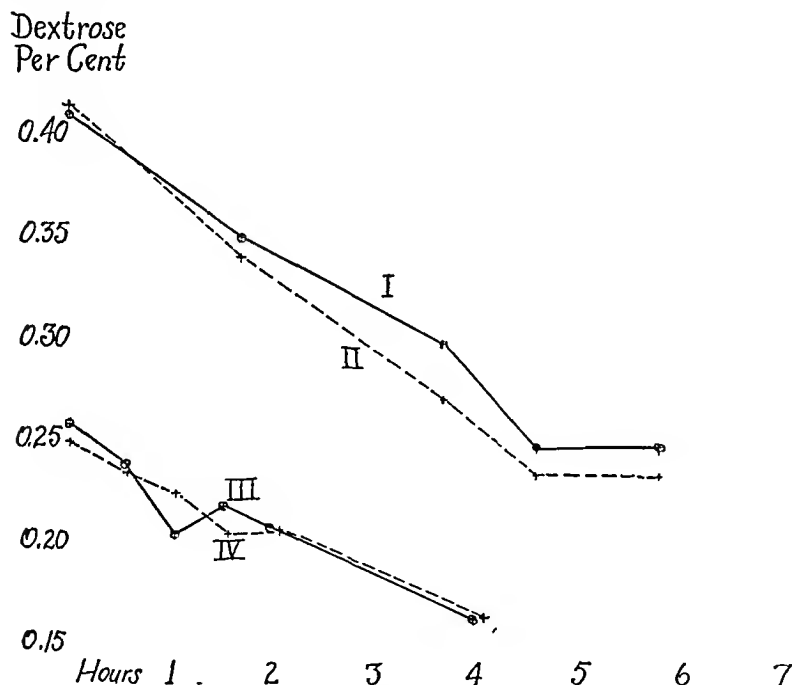


FIGURE 1.

I and II represent two dialyses of diabetic dog blood (from Dog 3) carried on simultaneously; I (solid line) had 1 mg. dry insulin added to 10 cc. of blood; II (broken line) contained no insulin. III and IV similarly represent simultaneous dialyses of two portions of diabetic dog blood (from Dog 4); III (solid line) contained 5.8 mg. of dry insulin in 22 cc. of blood; IV (broken line) contained no insulin. All four dialyzed against 0.15 per cent dextrose in Ringer's solution.

stopped in both cases, although the percentage of sugar was still well above that in the fluid against which it was dialyzing. The insulin added to I did not change the rate of dialysis, when compared with II. Curves III and IV, representing an experiment with blood from another diabetic

<sup>2</sup>A preliminary reference to this work was included in the report of Kleiner, I. S., and Bell, M., *Am. J. Physiol.* 90: 410 (1929), presented before the XIIIth International Physiological Congress, August 22, 1929.

animal, while not coinciding so closely, manifest the same general trend. Either could be considered a typical diabetic curve. Curve III (with insulin) not only is not more "normal" than IV, but even has a greater period of delay. There were very few experiments in which such simultaneous curves duplicated each other as closely as Curves I and II. This is not strange when it is remembered that the membranes used were of animal parchment, no two of which can be absolute duplicates. However in no case did insulin tend to increase the general rate of dialysis of the blood sugar or make the curve more uniform than that of the control, which had no insulin. This is true also for a single experiment in which human diabetic blood was employed.

It is thus evident that insulin does not produce its effect by any action which tends to make the blood sugar more diffusible. That is, if this phenomenon is due to the presence of glucose in combined form in diabetic blood, insulin does not break the combination.

The extensive literature on insulin affords no clear-cut evidence of any definite effect of insulin upon blood sugar *in vitro*. There is no agreement regarding its effect upon glucolysis; quite as many investigators find that it hastens glucolysis (2) as the reverse (3). Although our experiments can not fairly be considered true tests of glucolysis, still if insulin has a marked effect upon this phenomenon, it would be expected to influence these curves. Pico and Negrete (4) have stated that insulin increases the permeability of collodion sacs, Cuenca (5) reports that it permits of more rapid penetration of sugar into muscle, and Rona and Sperling (6) and Loewi (7) found that red blood cells take up sugar more easily under the influence of insulin. No similar increase in the permeability of the parchment membrane used by us was observed.

#### SUMMARY

Dry potent insulin, added to diabetic blood (dog's), has no effect upon the rate of dialysis of the blood sugar, nor does it have any apparent influence upon the permeability of animal parchment membranes.

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# CORTIN, VITAL HORMONE OF THE ADRENAL CORTEX\*

FRANK A. HARTMAN

University of Buffalo

BUFFALO

The cortex of the adrenal gland produces a hormone which is essential to life. Without it appetite fails, weight is lost and marked muscular weakness develops ultimately leading to prostration and death.

We have already described a method by which a dilute solution of this hormone can be prepared (1). The method is limited because the sodium chloride content determines the degree of concentration. An acidulated extract is saturated with NaCl. The hormone is carried down with the resulting precipitate. Ethyl alcohol (80 per cent) dissolves the hormone but coagulates the protein in this precipitate. The alcohol is removed by distillation *in vacuo*. Water is added to the residue to make the NaCl isotonic with the body fluids. Recognizing the limitation which the employment of NaCl put upon our product, we have been working on the use of solvents and are finally ready to report a satisfactory process.

## PREPARATION OF A CONCENTRATED EXTRACT

Any desired concentration of the hormone can be prepared by the following method: Cortical material is extracted with ether. After removal of the ether by distillation *in vacuo* the ether residue is extracted with warm 80 per cent alcohol which dissolves the hormone. Fatty substances are filtered off. Alcohol is removed *in vacuo* and the residue taken up with water to make any desired concentration. An extract almost free from epinephrin can be made by extracting the alcoholic residue with a small volume of ether.

Swingle and Pfiffner have also prepared a concentrated extract of the adrenal cortex (2).

We have previously suggested *cortin* as the name for the adrenal cortical hormone essential to life. For convenience we so designate it in this communication.

## CORTIN AS A SUBSTITUTE FOR THE ADRENAL GLAND

Cats with both adrenals removed have been furnished with cortin by subcutaneous injection. Eight cats have been so treated. The adrenals were removed in two operations in six and at one operation in two animals.

Cats whose adrenals have been removed in two operations survive indefinitely if treated with sufficient cortin. Of the series treated with

\*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

concentrated extract five are alive at the present time. The second adrenal was removed 39, 54, 61, 74, and 170 days ago, respectively. The sixth animal died at 41 days because the extract was discontinued, the intention being to let the animal pass into the last stages of insufficiency, then attempt to revive him. When the time came to revive him the extract used proved later to be both toxic and of no potency and therefore failed.

Of the two animals whose adrenals were removed at a single operation (by the lumbar path) one is alive at 28 days. The other cat lived 6 days but never recovered sufficiently to eat. She was a young cat that had had kittens a short time before.

All live cats are doing well, living a perfectly normal existence as long as we inject cortin in sufficient amounts twice daily. They eat as well as, or better than, normal. We know this to be true by comparison

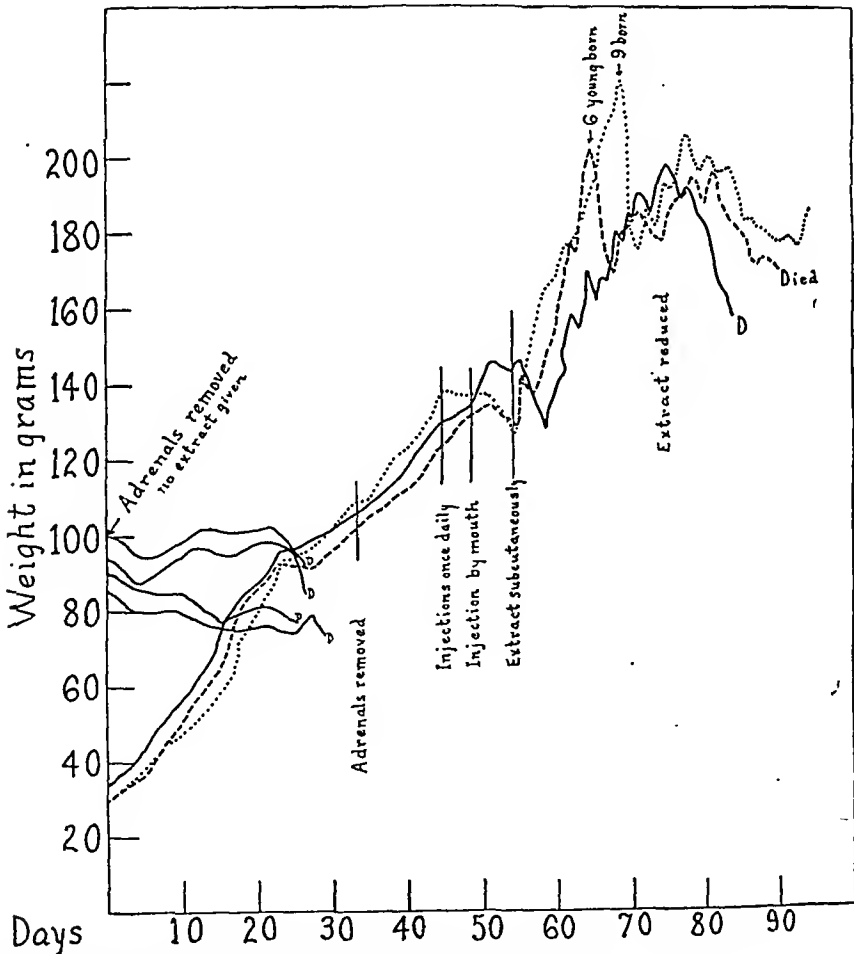


Fig. 1. Growth of rats before and after removal of both adrenals. Removal of adrenals at time indicated by arrow. Cortin injected twice daily.

with normal cats and in three of the animals we have daily records of the food consumption over a period of four months preceding the removal of the adrenals.

They gain in weight. Sometimes slowly, sometimes rapidly. This probably depends upon the individual and upon the amount of cortin administered. As an illustration, Cat RV weighed 2610 grams at the time of the second adrenal removal. At fifty-one days she weighed 2920 grams, a gain of more than eleven per cent.

In connection with the gain in weight, it is significant to point out that growing rats continue to grow unabated after both adrenals are removed if cortin is injected. Four rats of the same litter were injected twice daily with cortin after the removal of both adrenals. They continued to grow as fast as before the operation (Fig. 1). They also showed the activity of normal young rats.

*Blood urea.* Blood urea has been studied from time to time in all cats treated. When it becomes high, the injection of cortin lowers it. If low there is no effect (Table I).

TABLE I  
BLOOD UREAS IN CORTIN TREATED ADRENALECTOMIZED CATS

Cat	Days After Operation	Time of Day		Blood Urea mgm. per 100 cc.
OZ	15	9:00 a.m.	Cortin injected.....	68.4
		12:00 m.	.....	54.0
	18	9:00 a.m.	Cortin injected.....	84.9
		12:00 m.	.....	62.9
ON	Before	9:00 a.m.	.....	39.0
		12:00 m.	.....	45.0
	21	10:00 a.m.	.....	52.6
		1:00 p.m.	.....	57.2
	23	9:30 a.m.	Cortin injected.....	55.4
		12:30 p.m.	.....	57.7
RV	48	10:00 a.m.	.....	93.8
		12:30 p.m.	.....	92.3
	52	9:30 a.m.	Cortin injected.....	80.0
		12:24 p.m.	.....	58.0

*Behavior.* Adrenalectomized cats treated with adequate amounts of cortin behave like normal cats. They run, fight and play. One cat has been in heat. They show the usual interest in their surroundings, being alert and quick to respond to various stimuli. If cortin is reduced appetite fails, and asthenia develops.

*Resistance to infections and recovery from operations.* Untreated adrenalectomized cats show a low resistance to infections, often dying of respiratory infection. If they are operated upon recovery is unlikely or for a short time only, the ordeal reducing the survival period. Treated with cortin similar animals possess a high resistance to infection. Thus far we have had no infections of the respiratory tract. Two animals have recovered from extensive subcutaneous infections. One cat has been explored thoroughly for accessory cortical bodies while under the influence of ether. The opening was made at the mid-line and the ether was administered for 36 minutes. The animal recovered promptly and is still in good condition. No accessories were found.

As already indicated it is possible to remove both adrenals from a cat at one operation, the animal surviving indefinitely.

*Recovery from acute adrenal insufficiency.* We have succeeded in bringing back to normal health two adrenalectomized cats which were permitted to go so far as to become prostrate from lack of cortin.

Cat RM was in poor condition from having had an abortion. On three successive days she was very weak in the morning when first seen, each day being worse than the preceding day. On the third day she became prostrate. Convulsive twitchings and dyspnea were very marked. Cortin was injected intraperitoneally. In an hour the twitchings had ceased and the breathing had returned to normal. In seventy minutes she was sitting up and in one hundred minutes she was eating. By careful treatment she completely recovered and is gaining weight (64th day).

Both adrenals were removed from cat OZ at one operation. Although treated twice daily with cortin the feces became fluid and tinged with blood on the fourth day. Ten days after the operation an area on the skin of six square inches was discovered with a purulent discharge due to an iodine burn. The ordeal of dressing this region was too much. The cat later became prostrated, dyspnea set in and the extremities became cold. After two subcutaneous injections of cortin the cat recovered sufficiently to eat a little meat and drink some broth. However, it required six hours after the first injection to bring this about.

#### SUMMARY

We have demonstrated that a substance can be obtained from the adrenal cortex, which not only enables completely adrenalectomized animals to survive indefinitely in good health but to grow. This substance will cause recovery of cases of acute adrenal insufficiency. It also lowers the high blood urea of adrenal insufficiency.

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THE EFFECTS OF GROWTH PROMOTING AND GONAD STIMULATING PRINCIPLES OF THE ANTERIOR LOBE OF THE PITUITARY ON BASAL GASEOUS METABOLISM IN THE RAT\*

MILTON O. LEE AND JULES GAGNON

From the Memorial Foundation for Neuro-Endocrine Research  
Harvard Medical School

BOSTON

A considerable amount of work, both clinical and experimental, has been published on the effects of the anterior lobe of the pituitary body on the respiratory metabolism. The most of this work previous to 1928 has been cited by Raab (1) in his review on "Hypophysis and Metabolism," and need not be reviewed here.

In general, the greater part of the clinical evidence has indicated that in patients with anterior lobe deficiency there may be a slight decrease in the basal gaseous metabolism. In cases of hyperactivity of the anterior lobe, as in acromegaly, there is often a slightly increased metabolism. Rowe (2) from his wide experience with the use of several functional tests for determining over- or under-activity of the pituitary is in agreement with this majority opinion. Falta (3), on the other hand, has recently reaffirmed his belief that hyperactivity of the anterior lobe has a tendency to decrease the metabolic level. It is certain that clinically there are not seen the marked disturbances in metabolism with pituitary disorders that are characteristic of thyroid disorders. Indeed, Aub (4) and Boothby (5) have both expressed the opinion that there is little evidence that any part of the pituitary acts as a calorogenic agent, and point out the possibility that the apparent metabolic effects of the pituitary may be mediated secondarily through the thyroid.

Experimentally, Benedict and Homans (6) found that hypophysectomy in dogs resulted in a well marked decrease in the oxygen consumption and carbon dioxide production. These results have been corroborated by several later workers who have used this method of approach.

The obvious objection to both the clinical and experimental evidence is that it does not differentiate between the several active substances that are now known to be produced by the pituitary. It seems probable that there are at least two and possibly more hormone principles produced in the anterior lobe alone (Zondek, 7). In extirpation experiments, when all of these functions are destroyed, the effects may be quite different from those caused by the withdrawal of a single principle. In clinical cases, too, the evidence indicates that there is often an involvement of more than one function of the pituitary.

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In experiments on feeding anterior lobe preparations and the injection of various extracts, the results have also been difficult of interpretation, because of the fact that the potency, and even the particular principles contained, were not known. With the production of extracts of the anterior lobe with definite and assayable physiological properties, such as found by Evans and his co-workers for growth, and Zondek and Aschheim for sex gland stimulation, it has become possible to determine the metabolic effects more directly.

#### MATERIAL AND METHODS

Mature white rats, both males and females, were used as the experimental animals. These ranged in age from 4 to 8 months at the beginning of the experiment, and had shown normal growth and development. The animals served largely as their own controls, but other rats from the same colony stock, of the same age and living under the same conditions, were constantly being used in metabolic determinations and thus served as additional controls.

The basal metabolism was determined by the volumetric oxygen consumption method, with a four-unit, closed system apparatus somewhat modified from that designed by Benedict (8). For animal chambers squat pint jars were used, immersed in a water bath kept at such a temperature that the circulating air was constantly about 29.5° C. When respiratory quotients were desired the carbon dioxide was determined by weighing the proper absorption tubes. The rats were fed with bread and milk on the afternoon of the day previous to a metabolic rate determination, then at 4:00 P. M. the starvation period was begun. The rats were kept over night at a room temperature of not less than 80° F.

The next morning the rats were placed in the jars and at least an hour's rest period given. Metabolism determinations were then begun and continued for 4 to 7 hours. The starvation period was thus from 18 to 24 hours. Each determination represented the length of time for the animal to use 368.4 cc. (1 feed-pump stroke) of oxygen reduced to standard conditions. This time varied from 55 to 150 minutes, and hence from 3 to 6 determinations could be made in the course of the day on each of 4 rats. We have found that the first determination made in the day is often the highest and that the last ones of a long series are often high, a fact in agreement with clinical experience. The other determinations made during the day usually show close agreement, and in any case depend rather closely upon the amount of spontaneous activity which the rat shows. Ordinarily when in the lighted chambers at a temperature above the critical, the animals are content to doze lightly the most of the time. There are usually, however, a few periods of restlessness, washing, sniffing or scratching during the day. These movements are not recorded mechanically with our apparatus but each is noted by an observer in constant attendance. We have been able in almost every case to obtain at least one determination in the course of the day in which no, or only a very slight

amount, of movement occurred. For the basal metabolic rate on the particular day, the one, two, three or more such periods in which only the minimal activity occurred were usually averaged together. A critical analysis of the record is essential, because a rat may be entirely quiet during a determination, yet show an increased rate because of a fit of activity just before that determination began. In practice, our method of evaluating the primary data usually resulted in the selection of the lowest or the average of the several low metabolic rates determined during the course of the 4 to 7 hour period. These low determinations usually varied less than  $\pm 4$  per cent from their average, although the metabolic rates from week to week may show as much as  $\pm 8$  per cent variation from the average level in males and slightly more in females. The metabolic rates are expressed as calories per day per square meter of body surface.

A number of basal metabolic rate determinations were made for each rat before treatment with anterior lobe preparation was begun, in order to determine the normal basal level and the extent of the normal variations from the average. In 8 of the rats used, a long series of such control determinations had been made.

The growth promoting substances used were neutralized alkaline extracts of fresh beef anterior lobe, prepared after the method of Putnam, Teel and Benedict (9).<sup>\*</sup> Daily doses of 1 cc. were injected intraperitoneally for periods ranging from 15 to 72 days. Two periods of treatment with extracts were given in 5 rats, separated by rest intervals of 18 to 55 days. Four lots of extracts which had been found to be potent in promoting growth in control rats were used. Of these No. 3 was the most potent and No. 4 the least, judging from the growth response elicited. The average growth increase in the experimental rats on extract No. 3 was also the greatest. Extracts Nos. 1 and 2 were about equally potent and a little less so than No. 3. The extracts were not given over a sufficiently long period to produce "giant" rats, and probably the rate of increase in weight was not the maximum possible, since there were at least two 24-hour starvation periods each week for metabolism determinations.

Two sources of the sex maturity or gonad stimulating principle were used. One was an extract of sheep anterior lobe prepared by Parke, Davis & Company, the other was prepared by ourselves from the urine of women in the first five months of pregnancy, after the method of Biedl (10). The potency of the extracts used was assayed by testing on infantile rats as described by Biedl. Various dosages were used in the metabolism experiments, ranging from  $\frac{1}{2}$  unit once or twice a day to 6 units daily in two doses.

Two experimental procedures were carried out with both the growth promoting and the gonad stimulating extracts, one to determine the immediate effects of the extracts on the metabolic rate, and the other to determine the effects of continued daily administration.

<sup>\*</sup>We are indebted to Parke, Davis & Company for preparing and furnishing these extracts, and also the anterior lobe extracts containing the gonad stimulating principle.

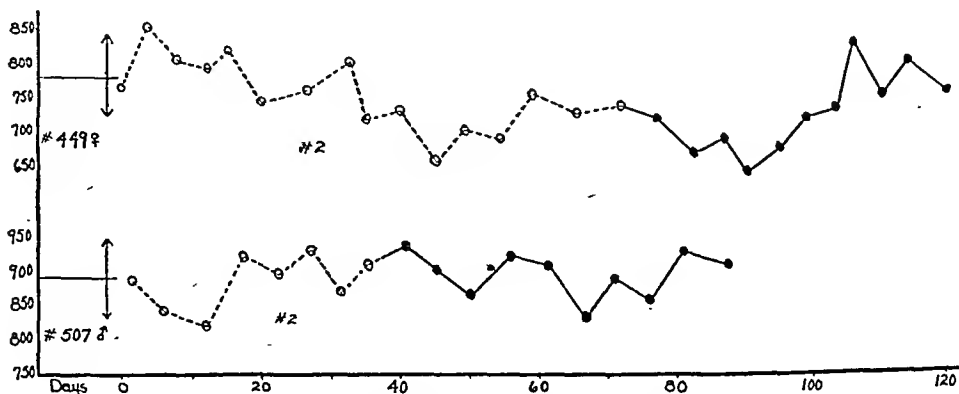
## RESULTS

*Growth Promoting Principle.* In studying the immediate effects of the growth promoting extracts, doses of 1 or 2 cc. were given intraperitoneally either after a preliminary metabolic rate determination on the same day, or to rats in which the basal level had been well established. The metabolic rate was then followed for 3 to 6 hours. Eleven such experiments were made with 7 animals, 4 females and 3 males. In 9 instances there occurred a definite increase in the heat production over the average basal level. This increase ranged from 6 to 17 per cent with an average of 10 per cent, and reached its maximum in 2 to 4 hours after the injection of the extract. In 2 experiments there was no apparent effect in response to the injection. In 4 rats similar determinations, made after the injection of *boiled* extracts in which the growth principle was destroyed, showed an increased heat production over the normal basal of about the same magnitude (5 to 13 per cent).

Almost any material, even saline solution or distilled water, when injected intraperitoneally, will increase the metabolic rate (Bacq, 11), and protein has a well-known specific dynamic action. These extracts contained about 10 per cent of protein and we believe that the increased oxygen consumption observed within the first few hours after intraperitoneal injections of the growth extracts, may be due to the dynamic action of the protein products and to the solution.

In the experiments on the effects of continued daily administration of the extracts, 18 rats, 7 males and 11 females, were used. In this series at least 24 hours elapsed after the injection of the extract before a metabolic rate determination was made, in order to obviate any specific dynamic effect.

There was a considerable variation in the metabolic responses of these animals, but a significant increase in the basal level was not found in any rat of the series either during the periods of treatment or afterwards. In 5 females and 3 males, or 40 per cent of the whole series, the extracts were



1. Effect of growth promoting extracts on the basal metabolic rate. The heat production is expressed as calories per day per square meter of body surface. The average normal basal rate is shown at the beginning, with the range of the variations indicated by the double arrow. The period during which the extract was given is shown by the broken curve.

apparently without any metabolic effects and the rates remained at about the same average level before, during and after the period of administration. The greatest single variations from the average levels in these 8 rats were +14 and -11 per cent, but such occasional variations are probably meaningless. It is perhaps significant that of these 8 rats showing negative metabolic effects, all except one failed to show growth responses to the extracts. Three females and one male received extract No. 4, which was found to be the least potent in promoting growth. In Figure 1, the individual determinations on male rat 507 are graphed. Extract No. 2, given daily for 38 days, had no significant effect on the metabolic rate, except for a suggestion at about the twelfth day. The graph for this rat is fairly typical of those for the other 7 which showed no metabolic effects.

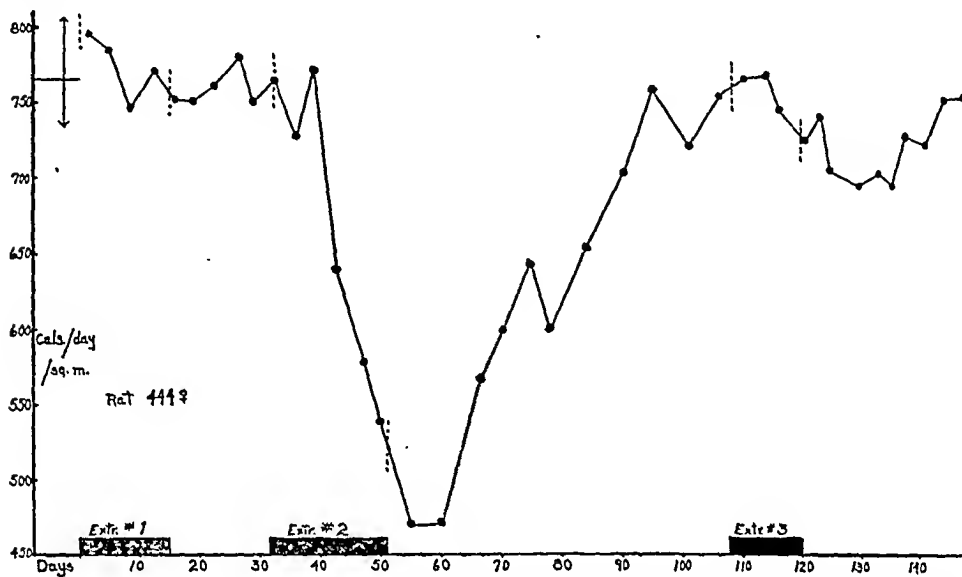
In 10 rats a significant decrease in the basal metabolic level was observed. In 4 females and 3 males this fall began during the period of administration of the extracts, but not until after several days' treatment had been given. In all experiments except one the metabolic rate fell to a lower level after the treatment with the extract had been stopped than while it was being given. In three rats the decrease did not occur until after the injections were stopped. In most cases the rate reached its lowest level in 6 to 18 days after stopping the extracts and then gradually rose again. This inertia in the metabolic response was a characteristic finding, and is suggestive of the metabolic response to thyroidectomy. The extent of the decrease for each rat is given in Table I, and the individual curves of 5 rats showing typical responses are given in Figures 1, 2 and 3.

TABLE I  
EXTENT OF LOWERING OF METABOLIC RATE IN RATS WITH  
GROWTH PROMOTING PRINCIPLE

Rat No.	Period of Treatment	Decrease During Treatment	Maximum Decrease After Treatment	Time Before Maximum Decrease
	Days	Per Cent	Per Cent	Days
500m.....	18	27	27	8
500m.....	18	?	None	?
503m.....	18	13	19	15
601f.....	18	None	16	8
601f.....	27	8	19	9
604f.....	48	None	18	14
444f.....	19	30	39	9
441f.....	11	?	10	9
449f.....	72	16	17	17
472m.....	26	12	16	12
17f.....	27	9	12	8
580m.....	23	9	11	15
455f.....	43	None	13	11

The most marked decrease in metabolic rate was shown by rat 444 (Figure 2). This female had an average normal metabolic level of 766 calories per day per square meter of body surface in 8 determinations, with extreme ranges of 735 and 807 calories. Extract No. 1 given daily for 16 days had no significant effect on the metabolic level either during the period or for 18 days afterwards (9 determinations). Extract No. 2

was then given for 19 days. Eleven days after the first injection, the metabolic rate was 640 calories—a decrease of 17 per cent. Seven days later it had dropped still further to 538 calories, or a decrease of 30 per cent from the normal basal level. The extract was then stopped and the rate in 4 days fell to 470 calories and 5 days later was found to have the



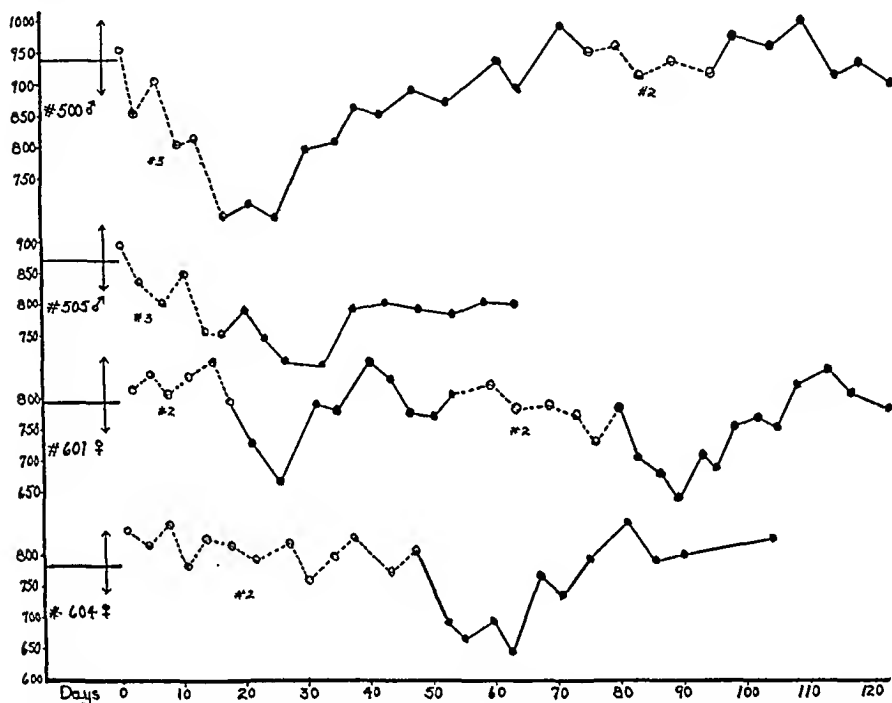
2. The effect of extracts Nos. 1, 2 and 3 on the basal metabolic rate of rat 444. The period of administration of the extracts is indicated by the heavy bars.

same value. This represents a decrease of 39 per cent from the original average level, and is the most extreme response we have found. There was then a slow, gradual increase in the metabolic rate, but apparently not to the original level. The few determinations made 6 to 8 weeks after extract No. 2 was discontinued would indicate that a new level had become established at about 740 calories. Extract No. 3 was then given for 11 days. It caused possibly a slight lowering of the metabolic rate. After stopping this extract the rate in 9 days fell to 694 calories and then in 14 days more gradually rose to about 750 calories.

Extract No. 2 was injected into female rat 449 (Figure 1), for 72 days. The average normal basal level was 778 calories. During the period with the extract there was a slight gradual lowering of the metabolic level. On the 45th day the lowest rate of 657 calories was recorded, or 16 per cent lower than the original level. This low level was not maintained, but after the injections were stopped, there was a further decrease for 17 days when the rate of 646 calories or —17 per cent was recorded. After this there was a gradual return in 2 weeks to about the original level.

Male rat 500 (Figure 3) showed a quick response to extract No. 3. Its average basal level in 7 determinations ranged from 883 to 1014 calories with an average of 940. One cc. of extract was given intraperitoneally for 18 days. Six basal metabolic rate determinations made during this period gave rates of 956, 853, 907, 805, 816 and 687 calories, or a maximum

decrease of 27 per cent. The injections were stopped and 8 days later the lowest rate of 685 calories or —27 per cent was recorded. There was then a gradual rise to approximately the original level over a period of 40 days. Extract No. 2 was then given for 18 days. There was no significant change either during or after the period of injection, although there is the suggestion of a fall in the rate during the time the injections were given.



3. Effect of growth promoting extracts on the basal metabolic rates of four other rats. Same conditions as in Figure 1.

Male rat 505 showed a response similar to but not so marked as that of 500 when given the same extract for the same length of time. The post-injection fall in metabolism continued for a longer time, 15 days. The lowest rate recorded was 703 calories or a decrease of 19 per cent from the original level of 871 calories. There was then a return to an apparently new and less variable level of about 800 calories. This rat acquired a pulmonary infection which prevented its being followed further.

Female 601, with a basal level of 793 calories, showed no decrease during an 18-day period of injection of extract No. 2. The 6 determinations made in this period, although higher than the average normal level, were all within 9 per cent of this level. Following the injection period there was a fall in 8 days to 668 calories or 16 per cent below the normal basal level. There was then a rise to approximately the original level in 10 days. The same extract was then given for 27 days and produced a slight lowering of the level. After discontinuance the rate decreased in 9

days to 642 calories, or —19 per cent, followed by a return in 16 days to about the original level.

Female 604, with an average normal level of .782 calories, showed a suggestion of an increased rate during 48 days of administration of extract No. 2. The highest rate recorded was 851 calories or only +9 per cent, however, and the preliminary basal level was based on only 3 determinations. In the post-injection period the rate fell in 14 days to 646 calories, or —17 per cent. It then rose in 15 days to a level of about 800 calories, which further suggests that the average level in the preliminary period is slightly low.

No significant changes were found in the respiratory quotients as a result of the growth promoting extracts. A total of 18 respiratory quotient determinations, during the period when extracts were given, showed an average value of 0.73, which is close to the average in control rats.

*Gonad Stimulating Principle.* Reiss and Winter (12), using extracts of the sex maturity stimulating principle from the urine of pregnant women, found no constant effects on the oxygen consumption, carbon dioxide production or respiratory quotient in rabbits. They used anesthetized animals, however, gave enormous doses (200 to 4000 units) of the material subcutaneously and followed the metabolism for only a few hours after each injection. We have used what are presumably more physiological doses, without anesthesia, and have followed the metabolic level during and after periods of continued daily administration. The results are given in Table II. Twelve rats were used, 9 females and 3 males. The extracts of gonad stimulating principle, both from anterior lobe and from the urine of pregnant women were given in doses of 1 to 6 rat units per day for 8 to 24 days. Frequent metabolism determinations made during and

TABLE II  
EFFECTS OF GONAD STIMULATING EXTRACTS ON METABOLIC RATE

Rat No.	Average Normal Basal Level	Gonad Stimulating Principle		Average Basal Level During Treatment	Average Basal Level After Treatment
		Units/Day	Days		
	Cals./Day/Sq. M.			Cals./Day/Sq. M.	Cals./Day/Sq. M.
Anterior Lobe Extracts					
280f.....	786	4	8	831	813
8f.....	717	3	9	740	701
477f.....	807	4	9	792	783
65f.....	752	1	9	740	745
20m.....	907	4	9	920	892
557m.....	840	2	8	835	815
Urine Extracts					
477f.....	783	3	15	776	759
450f.....	767	1	24	797	782
400m.....	774	3	24	785	766
355f.....	642	5	11	691	658
105f.....	701	4	11	742	710
401f.....	732	6	24	761	745
23f.....	681	4	24	660	665
557m.....	815	5	11	819	893
Average.....	765			778	760

after the period of treatment showed no significant changes from the normal level. The total average of the metabolic rates during the period of treatment was only 2 per cent higher than the normal average rate. Twenty determinations were made immediately following the subcutaneous administration of the extracts in doses of 2 to 8 units. Here again there was no significant change in the metabolism, although the tendency was towards an increased rate. The average rate in the 3 to 5 hours after injection was only 5 per cent higher than the normal average level.

#### DISCUSSION

The decrease in the metabolic rates as a result of the growth extracts does not seem to be sufficiently uniform to warrant the conclusion that the anterior lobe has an anti-calorigenic function. Although none of the rats showed an increase in metabolic rate, only 60 per cent showed significant decreases, and the responses in these varied from -10 to -39 per cent. There was apparently some rough correlation between the potency for growth promotion and the metabolic action. Extract No. 4, which was the least potent for growth, had no effect in 4 rats and only a slight metabolic effect in others. Extract No. 3, which was the most potent for growth, caused in every instance a fall in the metabolic level. Rat 444, however, showed a marked response to extract No. 2 and a much lesser response to No. 3.

The inertia of the metabolic response to the extracts was characteristic, the fall in rate beginning several days after the first dose of the extract, and continuing for some days after the injections were stopped. The growth response is also a slow one in rats, but apparently ceases within a day or so after the administration of the extract is stopped. Even with definitely potent extract, not all of the rats in a series show augmented growth rates and the same seems to be true of the metabolic response. The data are not sufficient to determine whether or not the effect on the metabolism is cumulative.

In general, the results substantiate those obtained in giant rats (13), in which the metabolic levels were found to be about 13 per cent lower than normal. They are also compatible with the results reported by Teel and Watkins (14), who found in dogs a marked drop in the non-protein nitrogen of the blood, and a decrease of urea and amino acids after injection of growth-promoting extract.

Without further data it is unprofitable to speculate as to the mechanism by which the growth-promoting extracts can cause a fall in the general metabolic rate. A number of bits of evidence, however, indicate that the thyroid may play some rôle in the mechanism, and further experiments along this line are being undertaken.

Our results with the gonad stimulating extracts supplement the observations of Reiss and Winter (12) on rabbits and indicate that in rats this material is without any general metabolic effect.



## SUMMARY

In adult rats the subcutaneous injection for periods of 8 to 24 days of 1 to 6 rat units per day of the gonad stimulating principle of the anterior lobe of the pituitary had no significant effect on the basal gaseous metabolic rate. Extracts both of fresh anterior lobe and of urine from women in the early half of pregnancy were used.

Ten rats of a series of 18 given daily intraperitoneal injections of growth-promoting extracts of anterior lobe for 15 to 72 days showed significant decreases in the basal metabolic levels ranging from 10 to 39 per cent. Eight rats showed no metabolic response. None of the animals showed an increase in the metabolic rate except when the determinations were made within a few hours after intraperitoneal injections. The fall in the metabolic rate appeared usually only after several daily doses of the extract had been given, and in most cases continued for 6 to 14 days after treatment with the extract had been stopped. Approximately the original levels were regained by most rats within 6 weeks.

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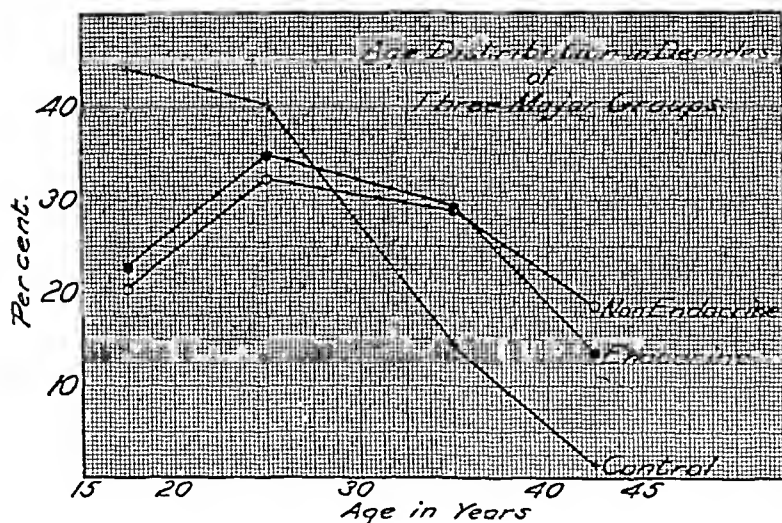
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## ENDOCRINE STUDIES. XXVI. AN ENDOCRINE INFLUENCE ON MENSTRUATION\*

ALLAN WINTER ROWE, Ph.D.

Evans Memorial,  
BOSTON, MASS.

It has long been recognized that the age of onset of the catamenia, together with the rhythm and amount after establishment, are all greatly influenced by a number of constitutional factors. Among these regulatory mechanisms the glands of proven internal secretion, in more recent years, have tended to assume an increasing significance. That ovarian function is important may be taken for granted, but the activities of both the pituitary and thyroid glands are now generally recognized as also real influences in determining the menstrual picture. The pancreas is omitted purposely from the present review but Joslin (1) notes a depressing effect of diabetes on menstruation and the occasional correction of amenorrhoea under insulin therapy. Both the adrenals and parathyroids are likewise excluded, since the number of proven cases we have seen is far too few to permit of informative statistical analysis. The endocrine significance of the thymus, pineal and spleen are, at best, questionable, and they find no place in the present discussion.



This paper deals with the correlation of menstrual disorders with a variety of disturbed endocrine functions and with certain disease states not primarily associated with the ductless glands.

\*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

The cases used for the study were selected from the records of a consecutive series of patients who had been carefully investigated by a diagnostic programme, described in detail elsewhere (2).

The data from all of the female patients between the ages of 15 to 46 have been collated, young children and women past the climacteric only being excluded. The composition of the several etiological groupings can be presented most compactly in tabular form.

TABLE I  
GROUP COMPOSITION

Group	Married	Unmarried	Total
Pituitary.....	149	193	342
Thyroid.....	98	108	206
Ovary.....	121	139	260
Total Endocrine.....	368	440	808
Non-Endocrine.....	203	223	426
Controls.....	250	275	525
Grand Total.....	821	938	1759

The pituitary cases were divided as follows: hyperfunction, 0.9%; dysfunction, 76.3%; and hypofunction, 22.8%. Similarly, the thyroid distribution was 8.7%, 32.5% and 58.8%, respectively. The ovarian cases were all hypofunctional. Group analysis in case of the first two series failed to disclose significant variations that might be attributed to different function levels.

But few words of explanation are necessary. The relatively predominance of ovarian cases in the endocrine group (nearly 1/3\*) is due to the fact that practically all of the gonad cases are in women, while groups of pituitary and thyroid cases show a very significant male representation. Further, as has been pointed out elsewhere (2-d), ovarian failure is seemingly confined to the years of maturity and thus young children have no part in the series.

The control group was made up of a series of young, unmarried women demonstrated to be normal by a searching physical examination and negative medical history. In addition, as the pathological groups comprised both married and unmarried women, and as the marital state is conceded to exercise some influence on the catamenial picture, a second control group was made up of a series of normal and demonstrably healthy, pregnant women drawn from the Maternity Service.

It will be noted that the distribution of married and unmarried subjects throughout the several sub-groups is about the same, hence any special influence of sexual activity is represented uniformly.

The "non-endocrine" group is composed of patients presenting initial suggestions of some hormone defect in history or physical examination but demonstrating on careful examination both an absence of endocrine involvement and the presence of some concrete disease state. The etiological scatter is a wide one, and the component members of the group are given in the next table (Table I-a).

\*The usual incidence in a complete series approximates 5:3:2 for Pituitary, Thyroid, and Gonads, respectively.

TABLE I-a  
ANALYSIS OF NON-ENDOCRINE GROUP

Group	Sub-Group	Number
Infections.....	Tuberculosis..... Arthritis..... Primary Focal.....	45
Mental and Nervous Disorders.....	Neuroses..... Psychoses..... Psycho-neuroses.....	54
	Central Lesions..... Epilepsy..... Parkinsonians..... Mental Retard..... Miscellaneous.....	60
Disorders of Metabolism.....	Obesity..... Malnutrition..... Gout..... Bone Diseases.....	27
Cardio-vascular Disorders.....	Cardiac..... Renal..... Cardiorenal.....	41
Blood Diseases.....	Primary Anaemia..... Leukaemia..... Haemophilia.....	9
Tumors.....	Malignant..... Benign..... Non-toxic Goiter.....	21
Disorders of.....	Eye..... Ear..... Skin..... Allergy..... Gastro-intestinal.....	78
Syphilis.....		25
Hepatic Dysfunction.....		43
Pelvic Disorders.....		12
Normal Controls.....		11
	Total.....	426

The ages of the patients were conditioned naturally by the onset and development of their presenting difficulties; equally, those of the married controls by the occurrence of the current pregnancy. The unmarried controls were drawn from groups of nurses and college students and, in the main, were under thirty years of age. The age distribution is represented graphically in the accompanying diagram.

A larger number of the control group were less than thirty years of age than was the case in both the endocrine and non-endocrine series; these latter showed an excellent correlation with each other. That the discrepancies of the control group were more apparent than real is shown by the average ages of each series, which were as follows: Pituitary, 28.6 years; Thyroid, 28.5 years; Gonad, 29.1 years, or for the combined Endocrine group 28.7 years. The average for the non-endocrine series was 29.8 years, and for the control group 24.1 years. The data, therefore, may be regarded as reasonably comparable.

In considering the age of onset of the catamenia it must be remembered that many of the endocrine and non-endocrine patients had certainly developed their presenting conditions in the years following the establish-

ment of menstruation. For this reason the figures recorded must be regarded as minima, and slight tendencies assume a significance disproportionate to their actual numerical values. To secure really authoritative data on this point it would be necessary to observe a series of children with active endocrine disturbances from prepubertal years until the time of maturation, recognizing further that in an appreciable number the spontaneous correction of the endocrine disorder would allow an onset of the catamenia at a conventionally normal age. From another standpoint this latter fact also is a factor in the reported late onset with individuals who present no active endocrine involvement at the time of examination. An earlier endocrine disorder may determine a delayed catamenia and then itself disappear, leaving apparently a normal function level. The whole problem of pelvic hypoplasia is intimately connected with this question as it is with that of sterility in later years.

Another uncertainty lies in the designation of the "normal" age for the catamenial onset. The literature is rich in conflicting observations, diet, climate, race, social conditions, and other factors superimposing active influences upon what may more strictly be designated as constitutional. In the wealth of anthropological data collected by Ploss and Bartels (3), every age from ten to eighteen seems to prevail as characteristic in individual selected groups. That the average for Caucasians dwelling in North America is somewhat lower than for the same racial strains in Europe would seem to be established. With the uncertainty existing as to the norm, it may be permissible to include here the records from this series as additional data bearing on the problem. All the patients in the present study were "Americans," i. e., Caucasians living in the United States, and with few exceptions were native born. The distribution, reduced to per cent for ease of comparison, is given in the next table (Table II).

TABLE II  
AGE OF ONSET OF CATAMENIA

Group	9	10	11	12	13	14	15	16	17	Over 17
Pituitary.....	0.6	1.8	7.2	19.5	33.7	19.8	7.2	6.3	2.4	1.5
Thyroid.....	1.0	1.5	8.3	16.6	33.7	21.5	6.8	5.8	2.4	2.4
Ovary.....	0.	0.	6.2	18.2	30.6	27.5	8.8	4.3	2.7	1.7
Total Endocrine.....	0.5	1.3	7.2	18.3	32.7	22.7	7.7	5.5	2.5	1.6*
Non-Endocrine.....	0.	1.4	6.6	15.2	31.6	26.5	9.7	5.2	2.4	1.4*
Control.....	0.	0.6	4.9	16.7	30.5	27.9	10.4	5.9	1.3	0.8*

\*17 at 18, 6 at 19 years.

The coincidences are more striking than the divergences. Three in every four in each of the three major groups matured between the twelfth and fifteenth birthdays, and again in each series over 90 per cent had established the menstrual function before sixteen. With just allowance for the relative values, it seems fair to assume that the function not established before sixteen, and less certainly before fifteen, may be regarded as delayed in onset. In other words, failure to mature by fifteen suggests the need of consideration, and by sixteen requires it.

No endocrine influence can be deduced from these data. While it is true that the percentage of endocrine subjects maturing after the eighteenth birthday is twice that of the control group, the average age of the latter within the conventional normal limits is somewhat higher than that of the former; the weight of the non-endocrine series approaches that of the control group. The average age of 13.5 years agrees well with the 13.9 years of Engelmann (4).

While the data from the mature cases fail to disclose any significant endocrine influence, the two points previously noted, *i. e.*, the onset of the endocrinopathy after maturity and the spontaneous correction of a pre-pubertal endocrine defect before or after the conventional age of onset, must not be forgotten. One is warranted only in the conclusion that data of the character given in Table II are not adapted to throw light on the question of an endocrine influence during the crucial years.

Somewhat more significant are the records of those patients who have failed to mature, although examined at an age when an established function might normally be expected. The present series contains a few such, and the significant facts are collected in the next table.

TABLE II-a  
MATURITY FAILURE  
(All Patients from 15 to 25 years inclusive.)  
NON-ENDOCRINE ETIOLOGY

Group	Number	Not Matured		
		Number	%	Ages
Pituitary.....	110	8	7.3	15, 15, 16, 17, 17, 18, 20, 24
Thyroid.....	78	1	1.3	17
Ovary.....	100	0	0.	
Non-Endocrine.....	125	5	4.0	15, 16, 16, 18, 21

Non-Endocrine Etiology		Ages
Two with Congenital Syphilis.....		16, 21
One with Tuberculosis.....		18
Two with Lesions of the Central Nervous System.....		15, 16

The inclusion of the cases at fifteen years is perhaps arbitrary, but their deletion would not affect the significance materially.

On the basis of chronological age only three, two pituitary and one non-endocrine case, exceed the upper limit of the control group. All of the patients in this list, however, gave numerous evidences of a retarded physical development other than failure of menstruation. The absence of ovarian cases rests upon the observation already noted that a primary failure of ovarian endocrine activity is seemingly an incident only of the years of maturity.

The figures given above warrant the conclusion that endocrine malfunction in the earlier years may produce a retardation of sexual development seemingly through a depressing influence on general growth activities. A similar influence is patently exercised by certain other conditions not demonstrably associated with the ductless glands. Parenthetically it

may be said that precocious puberty seemingly arises from hormone disturbances—the figures in Table II offer a very modest support for this thesis—but the dubious endocrine significance of certain of the alleged causal agents renders an exact allocation impossible at present.

With the menstrual function established, two characteristics demand consideration, *i. e.*, the interval of recurrence or rhythm of the period and the amount. Considering the first, it is generally recognized that the 28-day interval from the onset of one to that of the next period is characteristic. Equally, deviations from this accepted standard are frequently reported by seemingly normal women. An excellent review of the earlier literature is given by Novak (5), and the common report is of general regularity in from 70 to 75 per cent of the several series which have been investigated. Kelly (6) alone offers a significant exception in a record of 942 women of 1000 examined with a regular 28-day interval. In the figures quoted, regularity of function at an interval departing from the classic 28-day rhythm must be included. Taking the control group as a standard for later comparison, the data are collected in the next table (Table III).

TABLE III  
CONTROL GROUPS

Type	Rhythm					
	Nulliparous		Parous		Total	
Regular						
26, 27.....	5		7		12	
28.....	197	218	144	202	341	420
29, 30.....	16		51		67	
Less than 26.....	15		15		30	
More than 30.....	9	24	3	18	12	42
Irregular*						
Diminished.....	7		5		12	
Both.....	9	33	7	30	16	63
Increased.....	17		18		35	

\*In three cases irregular only in summer.

Menstrual irregularities are about equally common and similar among married and unmarried women, but the interval averages slightly longer in the married. Seventy-four per cent of the total control group show a regular 28-day interval, and 14 per cent more, regularity, but with a spacing greater or less than the mode. The fact that each person in the control group was demonstrated to be in good physical condition presumably accounts for a reported incidence of regularity higher than that noted in general community records.

Of possible irregularities there are obviously three types, with intervals diminished, intervals increased, and that form in which there is complete irregularity, both increase and diminution appearing in the interval as reckoned over a series of months. In the control group, increase in the interval is more frequent than the sum of the other two disturbances.

On the basis of the standards established by the control group, the data for the other series can be resolved and collected.

TABLE IV  
RHYTHM OF PERIOD

Group	Interval			
	Regular	Irregular		
		Diminished	Both	Increased
Pituitary.....	59.3%	9.9%	3.0%	27.8%
Thyroid.....	50.0%	12.6%	17.5%	19.9%
Ovary.....	59.6%	9.7%	3.1%	27.5%
Total Endocrine.....	57.0%	10.5%	6.8%	25.7%
Non-Endocrine.....	73.9%	7.6%	4.3%	14.2%
Controls.....	88.0%	2.3%	3.0%	6.7%

Here for the first time an unmistakable endocrine influence can be traced. This is patently referable to the fact that the menstrual habit and the endocrinopathy are observed coincidently and thus the errors unavoidable in the data on "onset" are eliminated. All of the endocrine series show a regularity significantly below the other two series—the thyroid the lowest at 50 per cent—and also below the usual report which is practically that of the non-endocrine group. Of the irregularities, the pituitary and ovarian groups show a dominant tendency toward a lengthened interval, the ratio to an abbreviation being 3 to 1. Only the thyroid shows a significant figure for the group showing complete irregularity, the cases indicating it nearly equalling in frequency those with delayed interval. This is a unique datum and defines a tendency characteristic of thyroid disorders which has been previously recorded (2-c). Where irregularity occurs the prevailing tendency is patently toward increase in the interval as the figures for all of the major series testify. To summarize, endocrine disorders tend to render the rhythm irregular with an increase in the interspace as the common expression. Thyroid disorders alone tend to produce a complete irregularity from four to six times as frequently as in the other series.

The amount of the period is less susceptible to exact expression. Both the duration in days and the amount of the flow come into consideration, and while the first can be reported with some degree of accuracy, estimation of the second scarcely falls in the realm of objective data. The personal hygiene and esthetic reaction of the individual influence so largely the number of napkins—the usual standard of measurement—as to make the report of but dubious significance.

Dealing first with the period duration in days, the reports in the literature (see Novak l.e.) show a wide scatter from the 4-5 day period of one group to the 2-8 allowance of another. That data should be comparable even though the limits selected be conventional and in some degree



arbitrary, an analysis has been made of the present control group reports and the final figures collected in the next table (Table V).

TABLE V  
DURATION

Days	Control Groups					
	Nulliparous		Parous		Total Number	
Less than 2.....	0	7	0	16	0	23
2.....	2		10		12	
2-3.....	5		6		11	
3.....	24	248	39	205	63	453
3-4.....	19		19		38	
4.....	57		53		110	
4-5.....	38		29		67	
5.....	67		39		106	
5-6.....	19		13		32	
6.....	24		13		37	
6-7.....	3	20	2	29	5	49
7.....	12		21		33	
Over 7.....	5*		6†		11	

\*Four at 8, one at 8-10.  
†Five at 8, one at 7-S.

The distribution here shows that the great majority of cases fall between the lower limit of an established 3-day period, and the upper boundary of not over six days. It is clearly recognized that these limits are arbitrary—for example, the seven-day report almost equals in number that for six days—but the abrupt changes in the curve make the limits selected reasonable. As all comparisons are relative and an absolute standard of the normal not yet established, the limits selected are serviceable since they apply equally to all the series under consideration. The combined data are given in Table V-a.

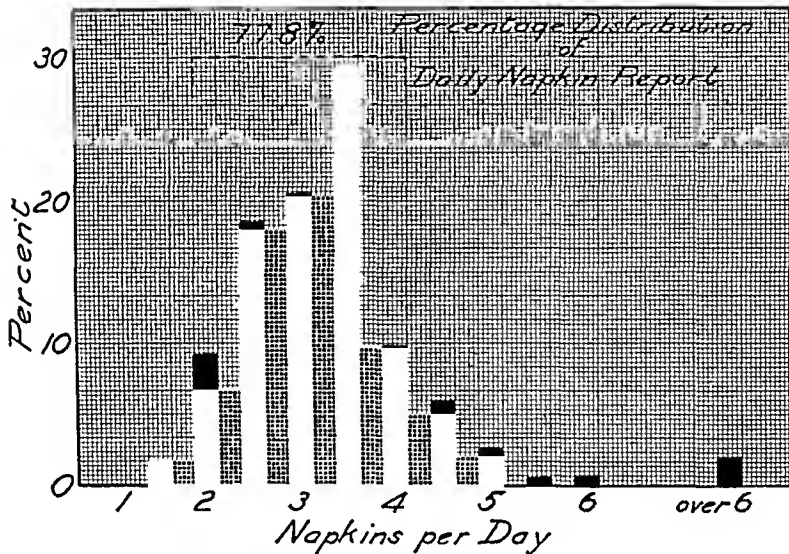
TABLE V-a  
DURATION

Group	Less Than 3 Days	3-6 Days	More Than 6 Days
Pituitary.....	12.3%	74.7%	13.0%
Thyroid.....	14.9%	73.2%	11.9%
Ovary.....	13.0%	69.2%	17.8%
Total Endocrine.....	13.2%	72.3%	14.5%
Non-Endocrine.....	10.2%	71.3%	18.5%
Control.....	4.4%	86.3%	9.3%

Both the endocrine and non-endocrine groups show a lower incidence of cases with conventionally normal duration than does that of the controls. The endocrine cases show an equal tendency toward diminution and increase, while the non-endocrine group emphasizes the latter type. A true endocrine influence is not clearly demonstrated by this datum but the facts point to a lowering of the frequency of normal duration through metabolic derangements arising from a wide variety of causes.

As was noted above, the actual quantity of the flow is influenced by so many extraneous factors as to be incapable of any exact estimation.

Analysis of the data from the control series, however, on the basis of the napkin report would seem to indicate that the majority of those composing the series use from eight to sixteen napkins per period. The accompanying graph illustrates the several habits in terms of number (Plate 2).



Such a division is arbitrary and thus open to criticism. The standard has the same degree of authority as that for duration, and as it affects all the series alike, with just recognition of the intrinsic limitations, it may be adopted as a first approximation.

TABLE VI  
AMOUNT OF FLOW

Group	Fewer Than 8 Napkins	Over 16 Napkins
Pituitary.....	20.8%	19.0%
Thyroid.....	27.5%	17.6%
Ovary.....	26.0%	26.0%
Total Endocrine.....	34.2%	21.4%
Non-Endocrine.....	17.1%	23.2%
Control.....	9.0%	14.2%

The figures here repeat in fair measure the indications already noted under the duration of the period. Both of the disease groups show a significantly larger percentage of cases falling either above or below the arbitrary normal standard. The endocrine group shows a slightly larger proportion of abnormal cases than its non-endocrine fellow, and with the tendency somewhat toward a scanty rather than a profuse flow. Again, the departures could as well be assigned to general poor health as to a specific endocrine agent.

The true measure of the period lies in the combination of the duration and the amount. A three-day period with four well-used napkins

daily approaches far more closely the normal standard than does a six-day flow which spots but one napkin a day. Further, the individual woman has criteria of performance based on her personal experience and that of her circle of friends, which merit consideration. In obtaining these data effort has been made to secure the opinion of each patient on her personal performance as well as the numerical data which have just been discussed. Collating the information from these several sources, the final figures are collected in the next table.

TABLE VII  
PERIOD ANALYSIS

Group	Decreased	Normal	Increased
Pituitary.....	29.0%	50.3%	20.7%
Thyroid.....	28.2%	53.9%	17.9%
Gonad.....	23.0%	53.7%	23.3%
Total Endocrine.....	26.9%	52.3%	20.8%
Non-Endocrine.....	27.1%	57.9%	15.0%
Control.....	9.1%	75.8%	15.1%

Considering that the criteria are uniformly applied throughout, these figures have some significance even though the sources from whence they derive are not to be regarded as unimpeachable.

The endocrine influence is unmistakable even though the effect of non-endocrine disease runs it a close second. In both the disease groups the prevailing tendency is toward a scanty period, an indication deriving added emphasis from the fact that the control group shows the opposite tendency. The figures as given are informative; they require no elaboration; an endocrine influence tending to produce abnormality would seem to be established.

There remains but one more consideration and that deals with the most subjective datum of the entire group.

Dysmenorrhea is a highly elastic term and its report of presence and degree depends upon widely varying individual standards. Taking the report of severe dysmenorrhea as the criterion, the occurrence in the several groups is as follows:

TABLE VIII

Group	Positive Report	Summary
Pituitary.....	17.5%	25.6%
Thyroid.....	18.5%	
Ovary.....	42.0%	
Non-Endocrine.....		26.7%
Control—Nulliparous.....	13.1%	8.0%
Control—Parous.....	2.4%	

The several indications are interesting. The higher value for the unmarried as opposed to the married controls accords well with the generally recognized influence of an active sex life. Together, the control group

shows but one-third of the frequency of report of either of the other two major series. Considered individually, dysmenorrhea is less frequently found in patients with pituitary or thyroid disease than in those with a variety of non-endocrine complaints although reported twice as often as by the control group. The large number of cases reported in the ovarian series is but one more expression of the egocentric nervous instability which characterizes the sufferers from ovarian failure.

### CONCLUSION AND SUMMARY

1. The menstrual histories of groups of women demonstrating three major endocrinopathies, pituitary, thyroid, and ovary, of a similar group presenting a variety of non-endocrine complaints, and of a control group comprising healthy married and unmarried females, have been analyzed.

2. Data obtainable by this method are not adapted to indicate the presence or absence of an endocrine influence on the age of onset of the catamenia. The reasons for this are indicated. An analysis is given showing that among Caucasians resident in the United States, the sixteenth birthday, and less certainly the fifteenth, may be regarded as the latest normal age for the establishment of the menses.

3. The few patients in the entire series who have failed to mature at an age when menstruation normally would be established, serve to indicate an active influence of the pituitary on menstruation.

4. An unmistakable endocrine influence is demonstrated in the determination of the rhythm of the function, all of the endocrinopathies tending to produce irregularity, with the prevailing type exhibiting an increase in the interval. The thyroid cases show a unique frequency in the report of a complete irregularity which may be regarded as characteristic.

5. Examination of the reports from the control group establishes a period of from three to six days, and an amount requiring from eight to sixteen napkins as the prevailing mode. On this basis the endocrine cases show a significant departure from the norm, which is only less strikingly exhibited by the non-endocrine series.

6. Any disease state seemingly increases the report of dysmenorrhea, the frequency being in the order of ovary, non-endocrine, thyroid, and pituitary disorders. The relatively high frequency of reports of dysmenorrhea in cases of ovarian deficiency undoubtedly derives in part from the marked nervous instability associated with the condition.

The writer wishes to express his thanks to Miss Mary McManus for assistance in compiling the data of the control group.

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## LIGATION OF THE TAIL OF THE PANCREAS IN JUVENILE DIABETES\*

GEZA DE TAKATS, M.D., M.S., F.A.C.S.  
CHICAGO

The regenerative power of the pancreas has been established by numerous clinical observations. Of all structures the ducts and islets are most resistant to local destructive processes and seem to have the greatest growth potential. Various pathological conditions, such as luetic pancreatitis of the newborn, acute pancreas necrosis and carcinoma of the pancreas destroy a great deal of pancreatic tissue. External secretion may suffer or completely subside in some of these conditions, as for instance in a carcinoma of the head of the pancreas, with compression of the duct. Whether the insular activity is insufficient or not will depend on the rapidity with which pancreatic destruction takes place. Thus in acute pancreas necrosis, high blood sugars and abnormal sugar tolerance curves are almost a rule, and glycosuria not uncommon. Gradually, however, sugar tolerance returns to normal (Jorns, 1; Sebening, 2). In Sebening's series all cases of acute pancreas necrosis showed a normal sugar tolerance at the end of six months. Sprengell (3) saw the hemorrhagic pancreas necrosis at operation and removed a large sequestrum of pancreatic tissue. When ten months later the patient died of an acute intestinal obstruction, only a slight fibrosis in the body of the pancreas indicated the residue of previous destruction. The patient was sugar free. Histologically there were numerous and very large islands. Knopfloch (4) reported the autopsy of an eighty-two-year-old patient, who had had an acute pancreas necrosis forty years before. There was a marked atrophy and lipomatosis of the organ, which could be explained by the findings of concretions in the ducts which obstructed external secretion. In the lipomatous organ, intact, well preserved islands were numerous. There was no glycosuria.

The loss of external secretion does not interfere with islet function. Recent post mortem observations of Baló and Ballon (5) emphasized the irritative action of retained pancreatic juice on the hypertrophy of islet tissue.

In patients afflicted with a carcinoma of the head of the pancreas, glycosuria is seldom observed and then only temporarily (Elösser, Kehr, Germershausen, 6). In Koch's case (6) the scirrhus carcinoma surrounded or pushed aside the islets but did not invade them. Distally to the tumor the pancreas was small and fibrotic. The islands were numerous and well preserved. Jorns (1) published four cases of primary carcinoma of the pancreas, verified by laparotomy, in which sugar tolerance curves are available. Two patients showed a normal alimentary hyperglycemia, one

\*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

patient with bone metastases and cachexia showed a slightly diminished tolerance curve. The fourth patient showed a normal fasting blood sugar and a hypoglycemia following ingestion of sugar (61 milligrams per 100 cc. at 45 minutes and 56 milligrams in two hours).

I have tabulated twenty-eight cases of carcinoma of the pancreas seen at Wesley Memorial Hospital, Chicago, between 1910 and 1930, verified by operation or autopsy. A glycosuria was present in only one case, that of a very obese patient who obviously had a true diabetes mellitus. Through the courtesy of Dr. R. H. Jaffé I was enabled to study two additional cases of carcinoma of the head of the pancreas. Both showed a complete atrophy of the acinar tissue with well preserved islets and proliferating ducts. There was no glycosuria in either of them (Fig 1). Even of more interest is a case of Dr. S. W. McArthur's of St. Luke's Hospital, Chicago, because the diagnosis of pancreatic carcinoma was made at exploration and verified later by autopsy. It was possible to obtain a normal sugar tolerance curve after the operation (Fig. 2) which is remarkable, as the autopsy (Case No.



Fig. 1—Lipomatosis of the tail of the pancreas with intact islands surrounded by strands of connective tissue. Case of Dr. R. H. Jaffé, Cook County Hospital.

15—1929, St. Luke's Hospital, Dr. Paul Breslich) revealed that the pancreas was converted into a tumor mass with the exception of a small segment at the head of the gland. These cases will be published in detail elsewhere.

The foregoing data seem to indicate an ample reserve capacity and regenerative power of the *human* pancreas. I have purposely emphasized them, as *experimentally* a hypertrophy and hyperplasia of islet tissue has been recognized and reproduced repeatedly. In a previous communication the literature on this subject was summarized (7). A great number of previous investigators have found that ligation of the pancreatic duct will result in atrophy of the secreting parenchyma, with a perseverance and

occasional hypertrophy of islet tissue. The idea, however, of turning the tail of the pancreas into a ductless gland by interrupting its external secretion and using the head and body of the gland to secrete pancreatic juice, belongs to Mansfeld (7).

In our own experimental work, an atrophy of the secreting parenchyma was induced by a ligature or complete separation of the tail. We showed histological evidence of a hypertrophy and hyperplasia of the islet tissue (8), a rapid cessation of the external secretion from the separated tail (9) and, corresponding to the histologic findings, an increased carbohydrate utilization (10). The increased sugar tolerance occurred three to four months after the operation and gradually subsided in the normal dog within the first year. Possible reasons for a lack of persistent increase in sugar tolerance has been discussed in a previous article (10).

I have mentioned adequate clinical evidence that patients of middle and advanced age show a remarkable regenerative power of the pancreas when the gland is suddenly or gradually destroyed by local processes. There is also experimental proof of a morphologic and functional hyperactivity of the pancreas when its tail is ligated. The question naturally arose, whether hypertrophy and increased islet function could be brought about in a case of diabetes. The islet hypertrophy might not occur in diabetes, and even if it did, the new islet cells might succumb to the same agent as the original cells. That a clinical trial became possible is solely due to Dr. Russell M. Wilder, Professor of Medicine at the University of Chicago, whose continuous support and encouragement materially aided the experimental work, and who selected from his large number of diabetic patients two diabetic children. The difficulties of management in juvenile diabetes were described by Wilder and his co-workers on a material of 190 diabetic children (11).

In a preliminary report with Wilder (12), we pointed out that children with severe diabetes, whose dietary and insulin control was precise and whose diabetes after the initial fluctuations had become stationary or progressively worse should be selected for operation. Accordingly, the first case was selected. I can now report on the later results in this case and add the second case, in which a modification of the original operation was carried out eight months ago.

*Case No. 1.* Thomas M., age 13 [detailed history in a previous communication (11)] fell early in September, 1921, and hit the back of his head on a cement pavement. He was apparently well the following day, but a month later began to urinate frequently. Next day large amounts of sugar were found in the urine. The blood sugar was said to be very high. A restricted "Joslin type" of diet was instituted. A month later the child shrieked with abdominal pain (acidosis?). A second physician then instituted the "Allen type" of diet. In February, 1922, the child was sugar free on a liberal diet. However, a mild attack of influenza and later a second bump on the head brought on sugar in the urine in large amounts.



From March 24, 1923, to January 1, 1929, the patient had six admissions to the Mayo Clinic. In 1923 he was 48 inches tall, weighed 44 pounds, was weak and emaciated. With a dextrose value of 100 he received 15 units of insulin. At the second admission the insulin had to be increased to 20 units. At the third admission, the blood plasma carbon dioxide combining power was 34 per cent by volume. The insulin requirement reached 40 units. This was in August, 1924. Later he developed an acidosis because of an abscessed tooth and infected tonsils. On July 5, 1927, the dextrose value of his diet was increased to 120, with 40 units of insulin. At his admission to Wesley Memorial Hospital on January 20, 1929, the patient had been steadily taking 40 units of insulin and taking

F. ST. CARCINOMA OF BODY AND TAIL OF PANCREAS

Oral sugar tolerance with 1.75 gms. dextrose  
per kg. body weight.

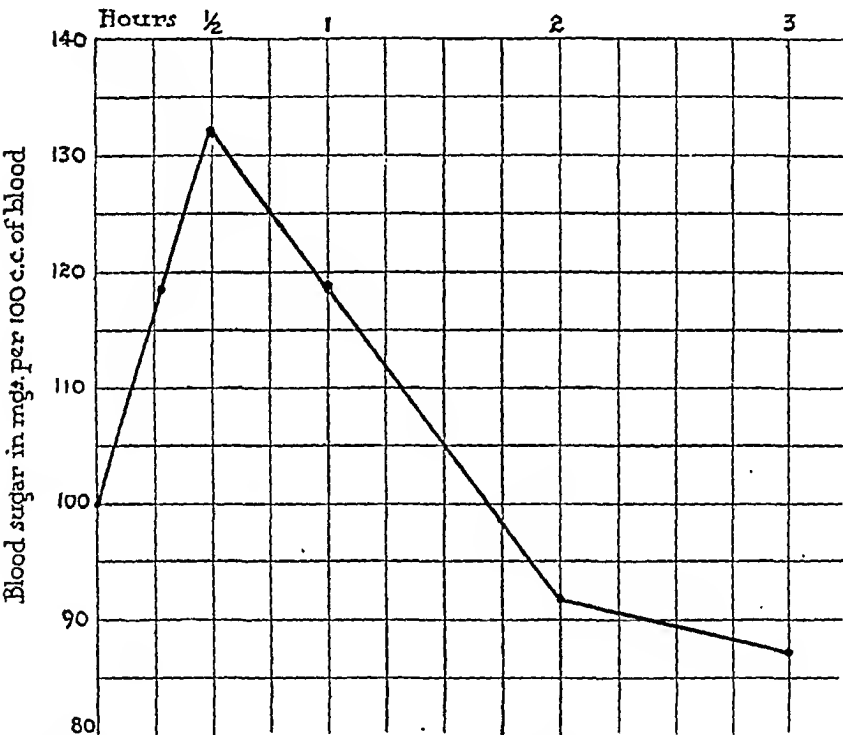


Fig. 2—Oral sugar tolerance curve in F. St., age 58, male case of Dr. S. W. McArthur of St. Luke's Hospital, Chicago. Patient's entire pancreas was transformed into the carcinomatous mass, with the exception of a small segment in the head of the pancreas.

a diet of carbohydrate 76 gm., protein 50 gm., and fat 150 gm., for the preceding two years.

The operation performed on January 21, 1929, has been described in detail elsewhere. A small hypoplastic pancreatic tail was divided with a high frequency cautery. He made a stormy convalescence, during which time drainage had to be instituted twice. He was discharged March 16, 1929, on the original diet taken before the operation, with 45 units of insulin. From March to May the insulin requirement remained steadily between 40 and 38 units. From April 26 on, insulin reactions began to

occur after the morning dose, which prompted a gradual reduction. On May 9, 110 days after the operation, the lowest level of 25 units was reached. From then on again the insulin had to be increased to 39-35 units, a stitch abscess of the abdominal incision having developed. On the week of June 4 the patient's diet was increased, as he still weighed only

## ISOLATION OF TAIL OF PANCREAS (Thomas M.)

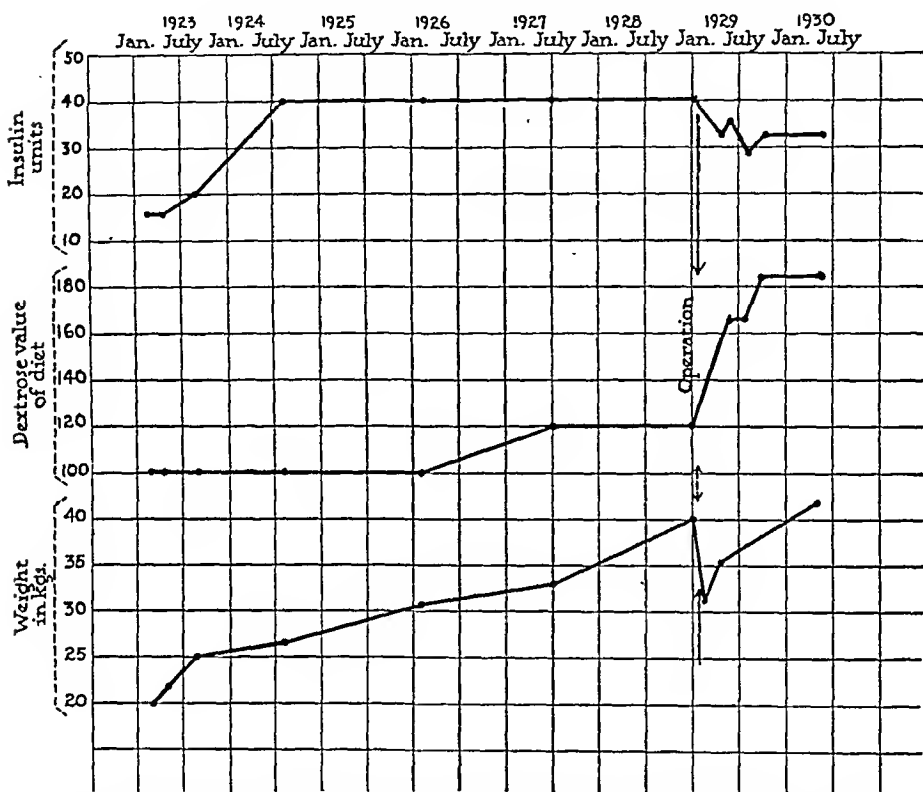


Fig. 3—Composite graph, showing the dextrose value of diet, insulin requirement and weight curve of Thomas M. The operation was performed on January 21, 1929.

80 pounds, as compared to 87 pounds before the operation. The new diet consisted of carbohydrate 102 gm., protein 75 gm., and fat 161 gm., a dextrose value of 166. On June 18, 1929, the insulin requirement was 39 units; on August 2, 29 units on the new diet. On May 31, 1930, seventeen months after the operation, the patient weighed 92 pounds (+5 pounds\*), was 57½ inches tall (+1½ inches) and takes a diet of carbohydrate 118, protein 85, fat 160, dextrose value of 183 (+63) with 32 units of insulin (—8).

*A severe diabetic child, whose previous history is well known, who has had diabetes of increasing severity for six years, was finally stabilized for two years on G. value 120, insulin 40. A year and a half after the opera-*

\*Figures in brackets indicate comparative data referring to the preoperative status. According to the latest report, patient's diet has been increased to a dextrose value of 200, without any increase in insulin.

*tion the patient is growing and gaining weight normally. While his insulin requirement is but slightly diminished, he is able to utilize an additional 80 grams of dextrose or its equivalent daily. Notwithstanding the small size of the isolated portion of the gland and despite serious post-operative reactions, the patient's diabetes has not become any worse and there is a moderate increase in carbohydrate utilization. This definite increase has occurred in a patient, who for six years had gradually lost tolerance, and who for the last two years before the operation had not shown any change at all.*

*Case No. 2.* Eugene G., age 16, patient of Dr. Russell M. Wilder. A detailed history will be published elsewhere. The family history is negative for diabetes. He had measles, mumps, whooping cough and tonsillitis prior to six years of age and tonsillectomy at the age of six. He was treated for tuberculosis of the cervical lymph glands for three years and three months at the Sunnyside Sanitarium, being discharged as well at the age of ten. Since then he felt well until the age of 14, when it was noticed by the parents that he passed a great deal of urine and lost weight. He suddenly became drowsy and five days later was admitted in diabetic coma to the Billings Hospital, with a fasting blood sugar of 250 mgm.,  $\text{CO}_2$  39-35 volume per cent and a white count of 22,600. On insulin-glucose treatment he promptly recovered and was discharged in November, 1927, on a diet of C 90, P 65, F 216, calories 2600, without insulin.

The basal metabolic rate was —18 per cent. The weight was 33 kilograms. Between this date and July 27, 1929, the patient had nine further admissions to the Billings Hospital. While he remained sugar free at first he gradually had to be given more and more insulin, but could not be well controlled. On June 4, 1928, while in the hospital, he developed acute appendicitis and was operated on by Dr. George M. Curtis. He was discharged twenty days later on a diet of C 100, P 75, F 225, 2725 calories, with 17 units of insulin before breakfast and 12 units before supper. Later he has had several upper respiratory infections, which always affected his tolerance. He had been careless about his diet, reduced his insulin several times, ignored his diet and was admitted with ketonuria twice. Finally, on his tenth admission, as he had done so poorly on a low carbohydrate, high fat diet, and continued to pass sugar on a diet of C 120, P 85, F 200, with 80 units of insulin, it was considered advisable to try him on a high carbohydrate, low fat intake. The carbohydrate was increased to 200 grams, the fat dropped to 100. The urine became sugar free and it was necessary to cut the insulin dosage to 40 units. The carbohydrate was then increased to 300 grams without increasing the insulin. When discharged, August 30, 1929, his diet consisted of C 300, P 75, F 100, G. value of 354, 2400 calories, with 45 units of insulin.

On October 1, 1929, the patient was admitted to Wesley Memorial Hospital, under the diabetic management of Dr. William H. Holmes (Case No. 147,279). While preoperative studies were made, he developed an

acute upper respiratory infection with a temperature of 103 degrees, which, however, quickly subsided. He was operated on October 18, 1929, with a preoperative diet of C 300, P 75, F 100, and insulin units 35-35-35.

Under nitrous oxide and local anesthesia the tail of the pancreas was exposed and a strip of fascia lata tied snugly around it. The operation will be described elsewhere in detail. The abdomen was closed without drainage and the patient made an uneventful recovery. He left the hospital in fourteen days.

On November 7, 1929, the patient on the same diet was taking 60 units of insulin. His weight was 42.3 kilograms, the height 159.9 cms. On November 18, he had abdominal cramps without rigidity. The leucocyte count was 9000; the urine was sugar free.

On December 17, on the same diet and 60 units of insulin, the patient weighed 46.7 kilograms. He received occupation in the hospital and from that time on received all his meals from the diet kitchen. On February 10, the insulin had to be reduced to 40 units a day, as he was getting severe insulin reactions. On February 25, he was readmitted to Billings Hospital because of an upper respiratory infection with a temperature of 101.1 degrees F. On February 27 he required 70 units of insulin, but March 3 it dropped to 35 units. During the following days the daily insulin varied between 45 and 50 units.

March 9, 1930, the diet was changed to C 69, P 50, F 215, with a G. value of 120. The insulin requirement fell to 18 units. This was its lowest point. The next week the insulin requirement started to rise and on March 23 chickenpox with an extensive eruption and fever was diagnosed. The insulin requirement rose to 50 units. On May 3, 1930, 100 grams of carbohydrate, 60 grams of protein, 206 grams of fat were allowed, which required 60 units of insulin. On May 20 he was persistently sugar free on this diet and insulin dosage. The body weight was 43.1 kilograms, the height 161 centimeters. On May 31, 1930, seven months after the operation, the patient weighed 43.1 kilograms ( $-0.6$  kilograms), his height was 161 centimeters ( $+1.5$  cms.). He was taking C 100 ( $-200$ ), P 60 ( $-15$ ) and F 206 ( $+106$ ) with insulin 60 ( $-20$ ).<sup>\*</sup> According to Dr. Wilder's comment on his present condition, there was evidence of improvement in his tolerance up to the chickenpox infection, after which, however, the tolerance grew worse and is now but little better, if any, than before the operation. It might be that the stimulating (high carbohydrate) diet, taken before and several months after the operation, was injurious to the islets undergoing hypertrophy, and it is for this reason that the patient was put back on a low carbohydrate, high fat diet.

*A diabetic child, whose disease is known to have been present for at least two years, and whose tolerance was rapidly growing worse, was operated on in October, 1929. Ligation of the tail of the pancreas was performed, the child making a rapid, smooth convalescence. Four months*

<sup>\*</sup>Since this article went to press, there has been a slow improvement in tolerance. The dextrose value is now up to 203; the insulin requirement could be diminished to 55 units.

after the operation, a reduction in insulin requirement took place. Five months after the operation, the high carbohydrate, low fat diet was changed to a low carbohydrate, high fat diet, with a corresponding large reduction in insulin. A little later a severe chickenpox infection aggravated the sugar tolerance. At present, seven months after the operation, and two months after the recovery from chickenpox, the tolerance, which had temporarily increased after the operation, is about the same as before.

In evaluating the result in these cases the following factors have to be considered:

Only years of close study will determine the end result. It seems, however, that in the first child, since whose operation more than a year

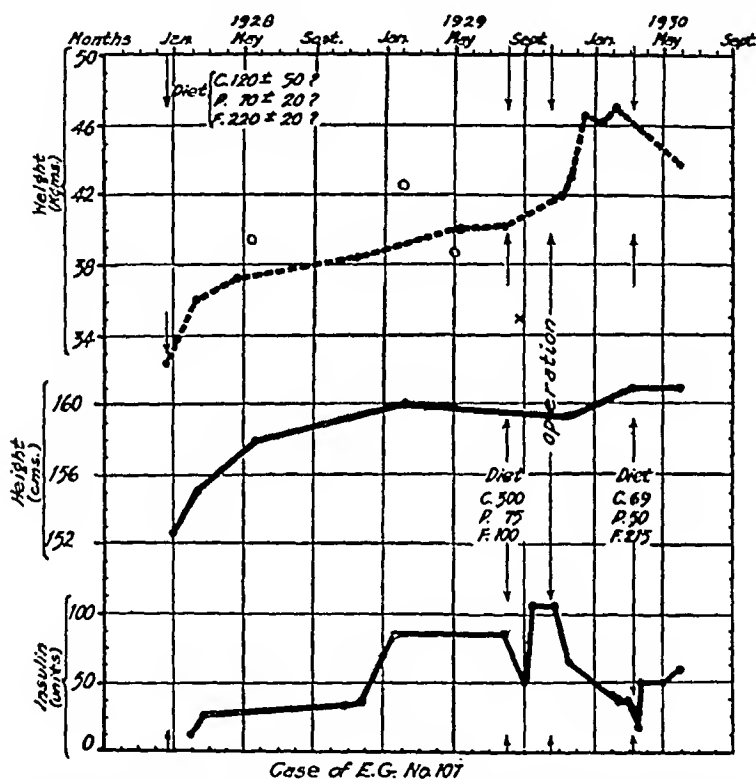


Fig. 4—Composite graph, indicating the diet, insulin requirement, height and weight curve of Eugene G. The operation was performed on October 18, 1929, during the Chicago meeting of the American College of Surgeons.

and a half have elapsed, is fairly stable now with 80 grams of additional dextrose and a little less insulin than before. When one considers that the tail end of the pancreas was abnormally short and that the postoperative convalescence was very stormy, even this modest improvement must be accepted as significant. In the second child, who had a large splenic pancreas, and in whom the modified operation (ligation instead of isolation) insured a far smoother convalescence, more marked results should have been observed. A fall in insulin requirement did take place, but the patient has up to the present time not recovered from the loss of tolerance which the chickenpox infection brought out. In a personal communication Dr. Russell M. Wilder has also pointed out that the high carbohydrate

diet, which had been given according to Porges and others to stimulate insulin production, might have been injurious and that better results could have been expected if the pancreas had been rested rather than stimulated in the period when the islets were undergoing hypertrophy. Sufficient time has not elapsed to permit a prediction as to the ultimate result in this case.

The parallelism between our animal experiments and the observations in the two clinical cases is striking. The change in tolerance is gradual, occurs around the fourth month and does not persist at its highest level but gradually returns to slightly above the preoperative level. The assumption that an islet hypertrophy takes place in the diabetic child could not be verified histologically, but seems very probably as spontaneous islet regeneration in diabetics has been described several times. It must be emphasized, however, that such an operation with resulting superregeneration of islets, does not hit at the real cause of diabetes, and that unless we shall succeed in protecting these new islets from injurious effects of nervous or hormonal origin, the new islets will not function any more efficiently than the original cells.

#### SUMMARY

1. Animal experiments have shown that there is a marked regenerative power of the insular apparatus of the pancreas. The islets undergo hypertrophy and hyperplasia, if parts of the gland are destroyed. Corresponding to the animal experiment, two diabetic children operated on showed a marked increase in tolerance, its maximum appearing around the fourth month.

2. For reasons that receive detailed discussion elsewhere, and are still being investigated, this improvement does not persist in its entirety, but a gradual decrease in tolerance occurs.

3. The future problem in attacking diabetes surgically lies not only in producing a hypertrophy of islets, but in protecting these islets from the continuous functional strain.

I wish to express my deep gratitude to Dr. A. C. Ivy, whose helpful suggestions have greatly aided my work and in whose laboratory the experiments have been conducted and are continuing. The operations were performed at Wesley Memorial Hospital. The diabetic management of the first case was in the hands of Dr. Charles A. Elliott, the second case was supervised by Dr. William H. Holmes.

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# THE PRACTICABILITY OF OVARIAN (AUTO-, HOMO- AND HETERO-) TRANSPLANTATION (WITH HISTOLOGIC PROOF)\*

MAX THOREK, M.D.

Surgeon-in-Chief, The American Hospital,  
CHICAGO

Since Knauer (1), in 1895, first successfully transplanted free ovaries from one site to another in the same animal, it has been abundantly proved by many other investigators, both experimentally and clinically, that ovarian transplantation, either as autografts or homografts, and to a more limited extent heterografts, is a practical surgical procedure. It has definite indications and when executed with proper technic it will in many instances give the desired results.

## EXPERIMENTAL OVARIAN IMPLANTS IN ANIMALS

1. *Autografts*: Knauer's successful experimental autografts were followed by many others, including those of Grigorieff (2), Uffreduzzi (3), and Benesch and Kohler (4). Long and Evans (5) made nineteen autotransplantations in rats, placing the implant in the mesometrium, omentum, spleen, etc. In fourteen of these the implant survived and functioned. Similar work has been done by many others. Some of the investigators found that the implantation of free ovaries in the uterine cavity was followed by pregnancy.

2. *Homografts*: Early work by Foa (6) and others showed that homotransplantation of ovaries could be successful, although not to the same degree as autografts. Pettinari (7), especially, showed that such implants would live, elaborate the normal internal secretion of the ovary and assume the germinal function. The literature showed quite clearly that pregnancy sometimes followed ovarian homotransplantation in spayed animals.

Opinions have varied considerably in regard to the functional results obtained from ovarian homografts as compared with autografts. Sand, Marshall, Athias, Pettinari, Lipschütz and others have found that with proper technic homografts were successful. Sand (8) performed twenty-four homotransplantations in rats. Four months later thirteen of these transplants were found to be functioning. He also performed twenty-nine ovarian homotransplantations in castrated male rats and in thirteen of these the transplant could be determined several months later. On the other hand, in fifty-two similar transplants in male castrated guinea pigs, there was only one feminization in the Steinaeh sense. As will be shown later, the site of the transplant and the technic of implantation have everything to do with the survival and function of the transplant.

\*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.



Tamura (9) (employing a special technic to be described later) in thirty-one experimental ovarian transplants from young female to adult male castrated mice, considered the result a success regarding the taking of the transplant, and found that when investigated at periods varying from ten to thirty-five days following implantation the transplants retained their typical ovarian structure, and that the germinal epithelium remained intact.

3. *Heterografts:* As a general rule, attempts at heterotransplantation of ovaries in animals have been failures. Lipschütz (10) believes that this is due to the difference in biologic relationship. After several years' experimental work in grafting ovaries from rabbits into the kidneys of guinea pigs, Lipschütz stated that he never had observed any endocrine effect from such transplants, nor a durable survival. I shall, however, have more to say on this point presently and hope to show that the possibility of successful ovarian heterotransplantation depends upon the closeness of the blood affinity between the donor and the recipient of the transplant.

The general conclusions to be drawn from the literature on experimental ovarian transplantation in animals are that autotransplants commonly survive and show secretional activity; that homotransplants are less successful, the success being in general a matter of technic; that heterotransplants commonly fail, both in regard to survival and function.

#### OVARIAN TRANSPLANTATIONS IN THE HUMAN SUBJECT

Morris (11), in 1895, was the first, after radical removal of the ovaries and tubes in a young woman, to transplant a piece of ovary to the stump of one tube. This woman became pregnant a month later. Such autotransplantation has been repeated by a number of investigators, commonly with success, but the technic of autoplasic free ovarian transplants has varied. A number of successful results have been reported following human ovarian homotransplantation.

In 1928 the author reported (12) upon forty-four personal cases of human ovarian homotransplantation. Thirty-six of these patients were traced and about 60 per cent of those who had suffered from exaggerated psychic and neurotic symptoms were completely restored to health. The other cases were ameliorated more or less. In five of these patients who were subsequently operated upon for abdominal condition there was an opportunity to examine the transplant one to four years after its implantation. In four instances it was found *in situ*, diminished in size but apparently surviving and well vascularized. No histologic examination was possible. My opinion, based on personal experience, is that ovarian homotransplantation is a practical surgical procedure which has definite indications, with a fairly well established degree of durability of results.

Among the clinical manifestations that may reasonably be ascribed to hypofunction of the ovary, Novak enumerates the following:

"1. Amenorrhea (absence of menstruation), hypomenorrhea (scanty menstruation), and oligomenorrhea (abnormally infrequent menstruation), delayed puberty and premature menopause.

"2. The vasomotor symptoms of the menopause (either natural or artificial).

"3. Some cases of sterility (probably only a small proportion).

"4. Possibly some cases of so-called primary dysmenorrhea, genital hypoplasia, obesity, repeated abortion, and menstrual headaches."

According to Hirst, sexual frigidity belongs in this group.

Norris and Behney (12a) recently have reported on thirty-one autotransplantations. They found that the majority of such implants "take" but that they probably do not survive more than two or three years. They believe that menopause phenomena when they occur approximate normal, even long after the transplant has disappeared.

Martin (13), in 1922, reviewed the literature of the subject and reached the general conclusion that while autotransplants gave some evidence of success in deferring the symptoms of the menopause and delaying the cessation of menstruation, homotransplants and heterotransplants gave practically no such evidence. I think that since the expression of this opinion much has been accomplished which would cause a modification of it. As a matter of fact, there are several circumstances apart from the nature of the transplant itself which are concerned with a successful outcome.

#### FACTORS CONDUCIVE TO SUCCESSFUL OVARIAN TRANSPLANTATION

I will assume that it is already proved that free ovarian tissue, no matter where implanted, if it survives and becomes vascularized, will continue to discharge its hormones and that these hormones will affect the organism about the same as that of the normal ovary in its proper situation. These remarks, of course, refer specifically to free ovarian transplants. They do not refer to pedicled transplants and the functional results are also modified by the presence or absence of the uterus or ovaries, or both, in the recipient of the transplant. Biedl (14) believed that a portion of one ovary in any part of the body sufficed for this function.

There are, however, many other factors which enter into successful implantation. These are: (a) The site of the implantation; (b) the technique followed; (c) the age of the implant; (d) the condition of the implant at the time of operation; (e) the blood affinity between the donor and the recipient. All these factors must be taken into consideration in connection with the fundamental conditions upon which survival of the implant and its functional activity depend—that is, its successful vascularization and the degree of activity of its germinal epithelium. If the transplantation is to be successful, proliferation of the germinal epithelium must begin soon after vascularization is definitely established. Keeping these matters in mind, let us consider the factors enumerated.

*Site of Implantation:* While, other things being equal, an ovarian transplant will "take" in many situations there are certain preferential sites. As early as 1907 Marshall and Jolly (15) described experiments in

which they transplanted ovaries into the kidneys of rats. The kidney was split, the transplant inserted and the kidney reclosed. This site was selected because of the rich vascularization. Lipschütz reports that since 1923 he has been transplanting ovaries into the kidneys of rabbits and guinea pigs, with definitely good results. He also has made a series of experimental homotransplantations, following the technic of Marshall and Jolly. In seventy-four such transplantations in guinea pigs sixty-four gave positive results. That is to say, 85 per cent of these intrarenal homotransplants proved successful.

In my extensive work on testicular transplantation, I decided that as an alternative to supraperitoneal transplantation the retrorenal space, between Gerota's capsule and the endo-abdominal fascia, should be very suitable for such transplantations and an improvement in the technic. After much experimenting this was found to be the case and a technic for this transplantation site was evolved and described in my book on "The Hu-



Fig. 1. Human ovary, transplanted perirenally (author's method) into *Macacus rhesus*. Refrigerated forty-eight hours.

man Testis" (15a), where it is fully illustrated. The vascular supply to this space is through the lumbar vessels. The transplant is deposited in this space without suturing. I have used this site in many of my clinical cases and experimental studies of ovarian homotransplants (Fig. 1). The

next best sites for implantations in clinical cases are the cervical and the suprapertoneal regions.

Tamura (9), reporting upon experimental ovarian homotransplantations in mice, recently has described a method of implanting the ovarian transplant on the surface of the kidney. His incision is made just posterior to the last rib, exposing the capsula adiposa and the kidney. The kidney is detached from the abdominal wall and the tunica fibrosa is incised and folded back. The implant is placed in the wound, the lips of the tunica fibrosa are pulled together as far as possible, the capsula adiposa replaced and the abdominal muscles and skin closed.

This technic differs from that of Marshall and Jolly and of Lipschütz only in so far that in the latter the kidney proper is split. It is only a

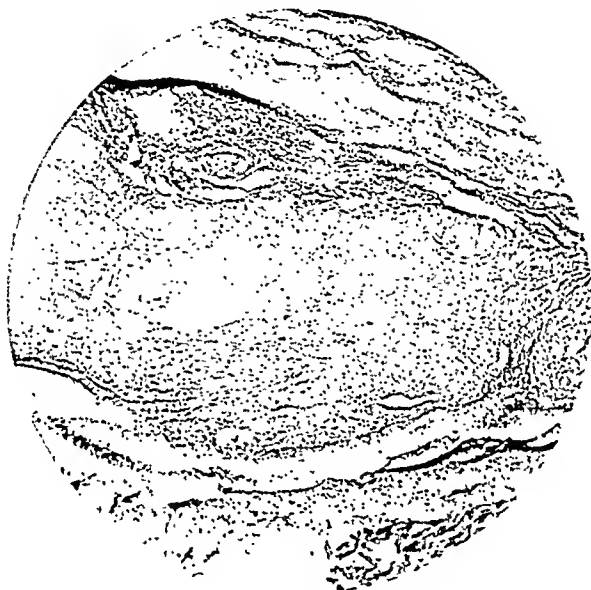


Fig. 2. Human ovary, twenty-four hours refrigeration, two months after implantation. X10.

variant of my original perirenal transplantation, and although it may be allowable for experimental animal purposes, as in the work of the investigators cited, it would be unsurgical for clinical purposes. My perirenal transplantation is thoroughly effective from the standpoint of vascularization; it is practical, simple, and offers no danger to the patient.

*Technic:* Ovarian transplantation should be executed under strict asepsis and with all surgical precautions necessary in any major surgical operation. This applies to both donor and recipient and it is best, if possible, to operate simultaneously on the donor and the recipient. Some, Steinaeh for instance, have expressed the opinion that some time should elapse between the removal of the ovary and its implantation. Lipschütz (10), however, maintains that intrarenal transplants have, in his hands, given just as good results when implanted immediately after castration as

when a certain time had elapsed. Ovarian tissue may, however, be preserved for some time in a refrigerator. Zondek and Wolff (17) kept human ovarian tissue at a temperature varying from zero to  $-12^{\circ}$  C. and after five days transplanted it into an amenorrheic patient who, two months later, menstruated. The researches of Lipschütz (16), nevertheless, leave no doubt that ovarian tissue dies at a temperature below zero. Other authors have found that freezing the implant injures it and that if such material is transplanted it fails in its endocrine function. Lipschütz,



Fig. 3. Position of human ovary refrigerated ninety-six hours and transplanted supra-peritoneally into *Macacus rhesus*. Three months after transplantation.

however, found that ovaries preserved in ice did function. In twelve intrarenal transplantations in which material which had been kept in ice for from one to three days was used, six positive results followed in animal transplantations. The proportion of successes diminished the longer the ovary was kept at low temperature before being transplanted.

In my refrigeration experiments extending over a period of a year I have found that good results have been obtained only when the time of refrigeration of the transplant, human or ape, did not exceed ninety-six

hours. If a transplant preserved for a longer time than this was used failure resulted. Lipschütz considers that a transplant kept at a temperature of from 1° to 3° C. will preserve its vitality up to sixteen days, and that if transplanted it will survive and function endocrinologically (Figs. 2-3).

*Site and Condition of the Implant:* For good functional results it has generally been considered that the transplant should be removed from a young donor, although Lipschütz and Tamura both report good results



Fig. 4. Human ovary transplanted into *Macacus rhesus* (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain.

from the transplantation of adult ovaries. A whole or half of an ovary may be used.

It goes without saying that the ovarian tissue to be transplanted must be in a healthy and functioning condition, but an ovary whose function in the donor may have been deficient or failed because of some systemic condition may function satisfactorily in its new location in the recipient. Furthermore, an infantile ovary may give normal function when transplanted. Lipschütz showed that in guinea pigs an immature ovary

functioned endocrinologically when transplanted into castrated adult animals, but if transplanted into immature castrated animals the endocrine effects are not apparent until the animal arrives at the age of puberty.

When an ovary is transplanted into a castrated male guinea pig the Graafian follicle shows a tendency to enlarge but a corpus luteum is never found. On the other hand, in a castrated female such a transplant almost always shows a corpus luteum. It has been observed that in a normal

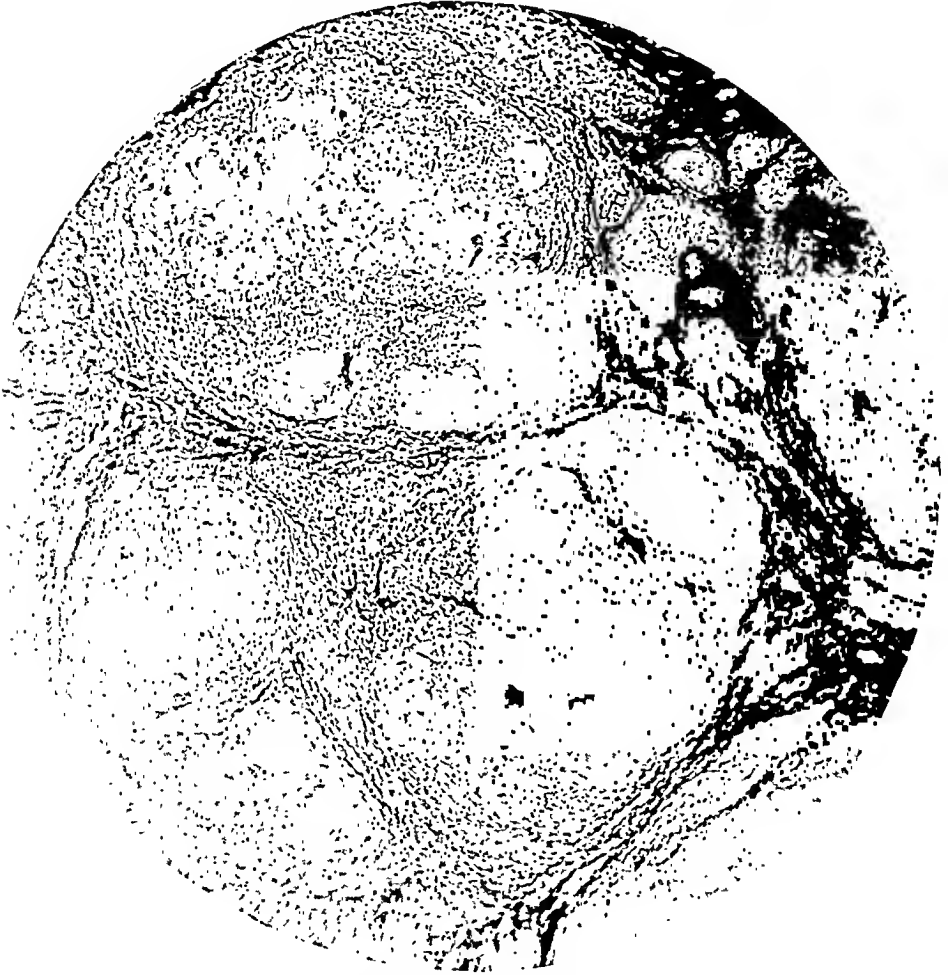


Fig. 5. Human ovary transplanted into *Macacus rhesus* (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Atretic follicles.

woman with both ovaries functioning *in situ*, if a third ovary is implanted and "takes" no corpus luteum is ever found in it; but in the majority of castrated women in whom a transplantation is carried out, corpora lutea can be demonstrated in the implant.

*Blood Affinity:* The success of organ and tissue transplantation in general varies directly according to the difference in blood affinity between the donor and recipient. Moorehead (18) recently referred to experiments by Staige Davis showing the possibility of *matching or typing tissues for implantations the same as the typing of blood*. Such implants

*Davis terms "isografts."* In sex gland transplantations the degree of blood relationship between the donor and recipient is a matter of prime importance. In my book already cited I pointed out (Chapter xiii, pp. 327, et seq.) the value of Nuttall's verification of the affinity of human and certain anthropoid bloods, the highest type of affinity being between the bloods of Cercopithecoidea and Simiidea. This close affinity which seems to substantiate Darwin's conception, so far as tissue relationship is concerned, was advanced as a reason for the success of testicular transplantations between man and the higher anthropoids, and vice versa.

These remarks apply also to ovarian transplantations. Furthermore, it may be said that even in homotransplants the matching of the blood of the donor and the recipient is important. Both should be of the same blood group to insure the best results.

3. *Heterografts:* The literature contains only a few reports regarding ovarian heterotransplantation in the human female.

The above remarks regarding technic, blood affinity, and so forth have particular reference to heterotransplants and naturally lead to my own work on ovarian heterotransplantations, which I desire to report in this paper.

#### AUTHOR'S PERSONAL WORK ON OVARIAN HETEROTRANSPLANTS

Apart from clinical ovarian homotransplants, I have during the past three years conducted a series of experiments having for their object the possibility of an interchange by transplantation between various glands in mammals, including the human species.

One set of these experiments dealt with the transplantation of human ovary tissue into *Macacus rhesus* monkeys. I submit herewith the histologic proof of the successful result of an ovarian implant from the human to *Macacus rhesus*, observed for eleven months after its implantation. This is, so far as I know, the first complete proof of such a successful heterotransplantation from human to *Macacus rhesus*. The histologic illustrations (Figs. 4-10) show all the elements of the transplanted ovary preserved for eleven months, with the exception of primordial ova.

Lipschütz states that Veronoff speaks in the lay press of the implantation of a human ovary into a castrated *Macacus rhesus*, following which the animal menstruated. No histologic proof is offered as to the condition of the implant, nor is a report made in any scientific publication.

Commenting upon this experiment Lipschütz remarks that, if ethically permissible and if human material is available, this experiment should be repeated, but that results will only be impressive if two fundamental conditions are fulfilled, namely, (1) that the suspended genital functioning of the host (all the sexual cycle phenomena in the ape) is resumed; and (2) that the microscope must without any doubt show the surviving transplanted ovary with exclusion of the possibility of any small portion of the true ovary remaining behind. The practical importance of the whole question is so great that the experimental proofs should permit of no equivocal



in the early stage of its formation. Combination forms are common.

The clinical significance of the ovarian hyalinization requires further comparative studies.

I wish to express my appreciation to Dr. M. A. Goldzieher for his kindness in examining the microscopic section described here. His findings were as follows:

"The section of the ovary, stained after van Gieson, reveals a lobular structure as the result of hyalinized connective tissue septa, separating areas of different size and shape. This hyaline connective tissue is obviously the product of an ordinary process of scarring and the hyaline itself is derived from the collagenous fibrils which again are produced by fibroblasts.

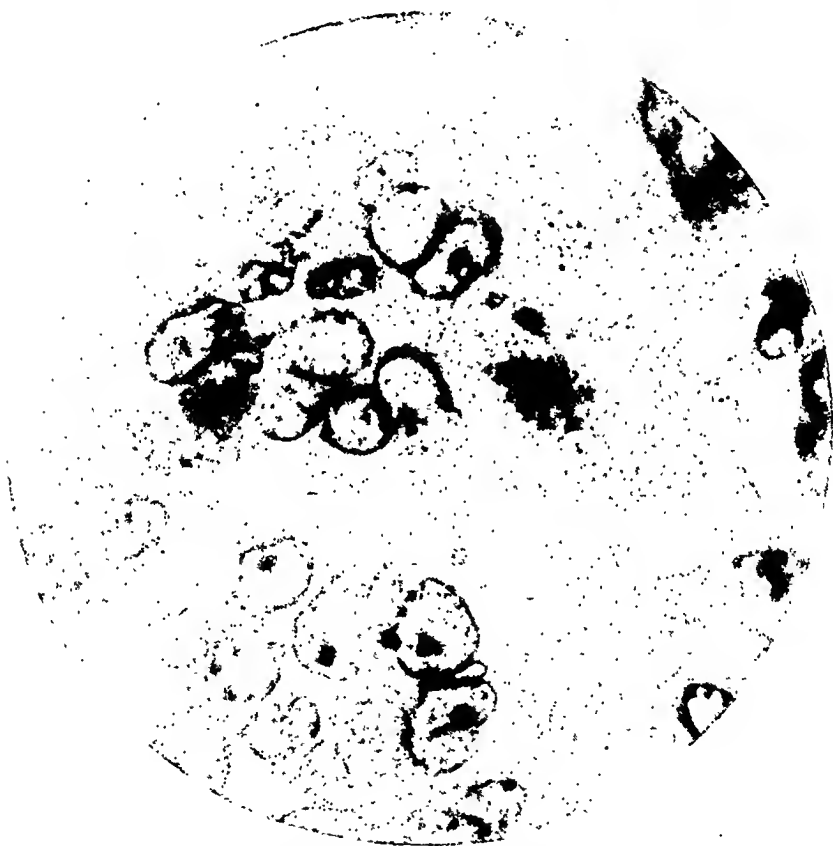


Fig. 8. Human ovary transplanted into *Macacus rhesus* (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Follicular cells simulating multinuclear giant cells.

"Within the lobules, we find peculiar, large cells with a remarkable tendency of forming giant cells. They are surrounded by more or less massive granulation tissue and occasionally by groups of polynuclear leucocytes. These cells have a remarkable tendency of forming structures vaguely suggesting lutein bodies. These cell groups are oval or triangular and sometimes show a peculiar wavy character. The center of these structures contains what appears to be hyaline material, most of which, however, stains yellow while bright red hyaline is less conspicuous. It is my impres-

sion that the yellow material derives from a combination of necrobiosis, fibrinous exudation and compares well with the processes, which are met with in the involution stage of the lutein bodies.

"There are other hyalinized areas which stand out particularly well in some of the H and E sections. This extensive hyalinization is of a peculiar trabecular character. Between the hyaline trabecles cells are pres-

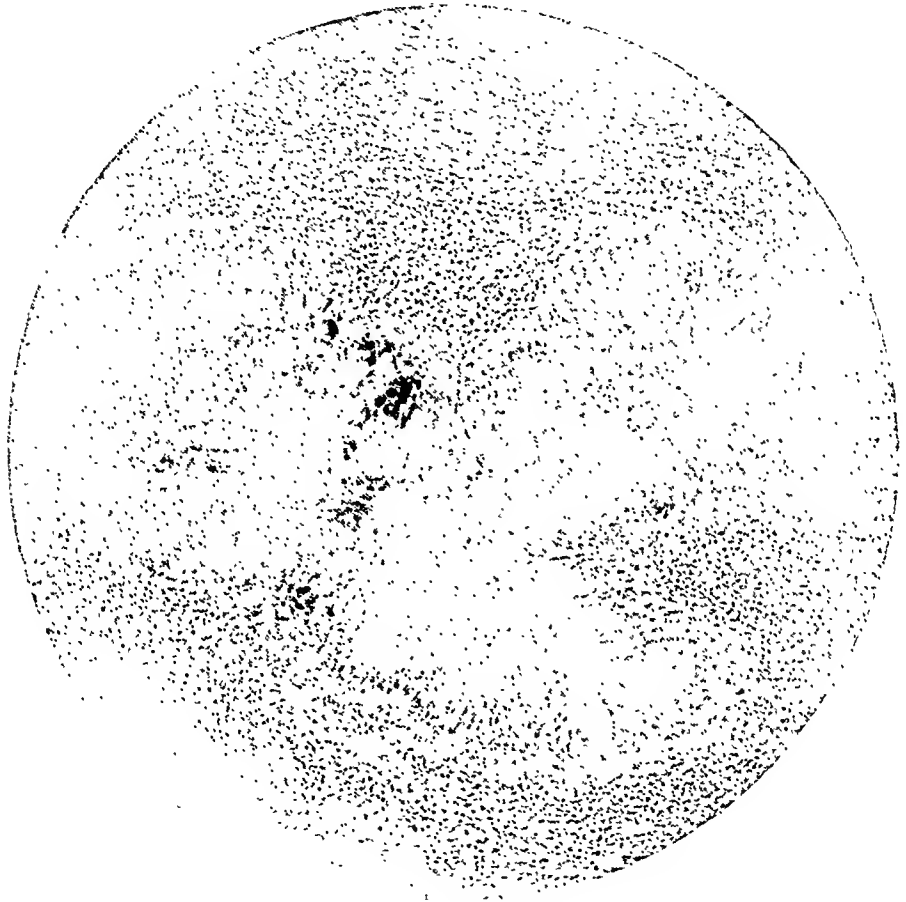


Fig. 9. Human ovary transplanted into *Macacus rhesus* (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. Corpus albicans (area of hyaline degeneration) or corpus luteum?

ent which are of the type of the ovarian interstitial cells, although their nuclei are sometimes somewhat larger, vascular and not very different from those seen in the large or giant cells described above. The similarity is enhanced occasionally by the identical behavior of the nuclei. Yet, as a whole, these cells are different and have no tendency to form giant cells.

"This type of hyalinization is morphologically identical with that observed in the ovarian stroma which I have described as independent from follicles or lutein structures.

"It is my impression that the large cells, including giant cells, derive from granulosa cells and the hyalin masses about which they often center are products of necrosis, exudation and perhaps secretion. The other type of hyalinization is definitely interstitial and indicates a similar metabolic disturbance of the interstitial cells to that which we find so frequently in ovaries removed with fibroids of the uterus.

"As a whole, the changes observed are, besides an inflammatory component, mostly of a regressive character. Yet, it seems that many of the specific cells of the ovary are in a state where they might be still capable of surviving and producing hormone effects."

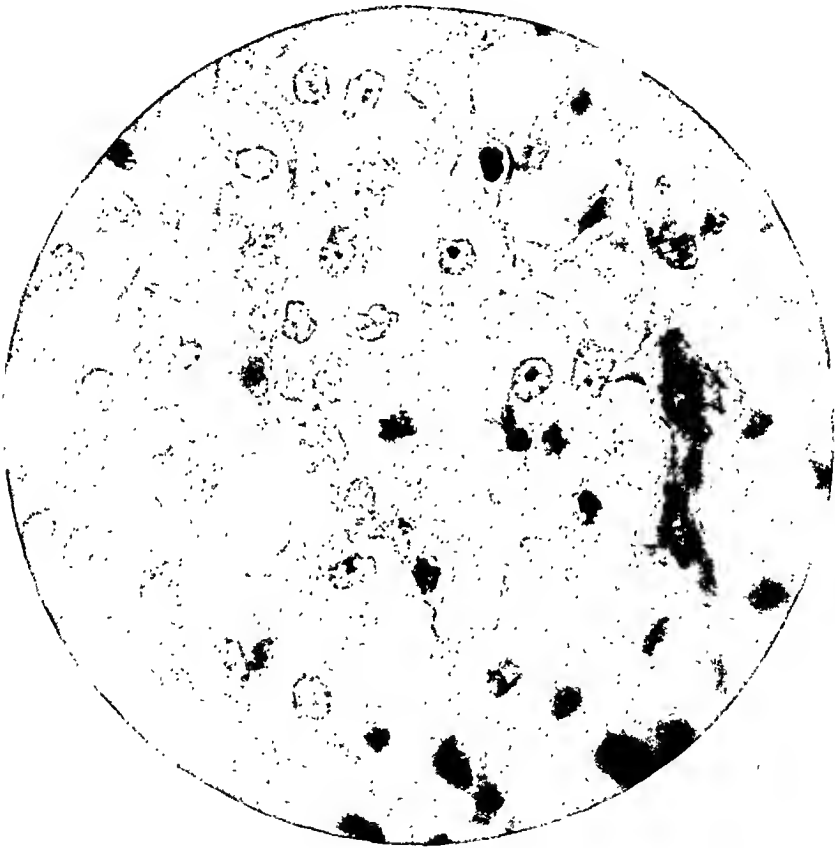


Fig. 10. Human ovary transplanted into *Macacus rhesus* (neck). Refrigerated twenty-four hours. Eleven months after implantation. Van Gieson stain. "Lutein cells" or lipid containing cells in hyaline degenerated areas.

*Comment:* What has been described apparently represents different stages of follicular atresia and corpora lutea involution. Connective tissue invasion from the mesenchymal tissue of the neighborhood did not seem to have played an important rôle. The presence of corpus luteum cells persisted after eleven months with well defined cell characteristics and excellent stain affinities. Hyaline changes observed in the adult ovary were not found in the transplanted embryonic ovary (Figs. 11 and 12).

Knauer and Steinach (21) reported the survival of animal ovarian autotransplant for three and one-half years, respectively, and Maulelaire

## THOREK

(22) and Natrass (23) saw such transplants living for eight and nine and one-half years after implantation in the human subject. In my clinical homotransplants as already stated, they were found to be functioning at periods varying from one to four years after implantation. Athias (24), in his animal ovarian homotransplants, found that follicles were histologically recognizable in the transplants two years after implantation.

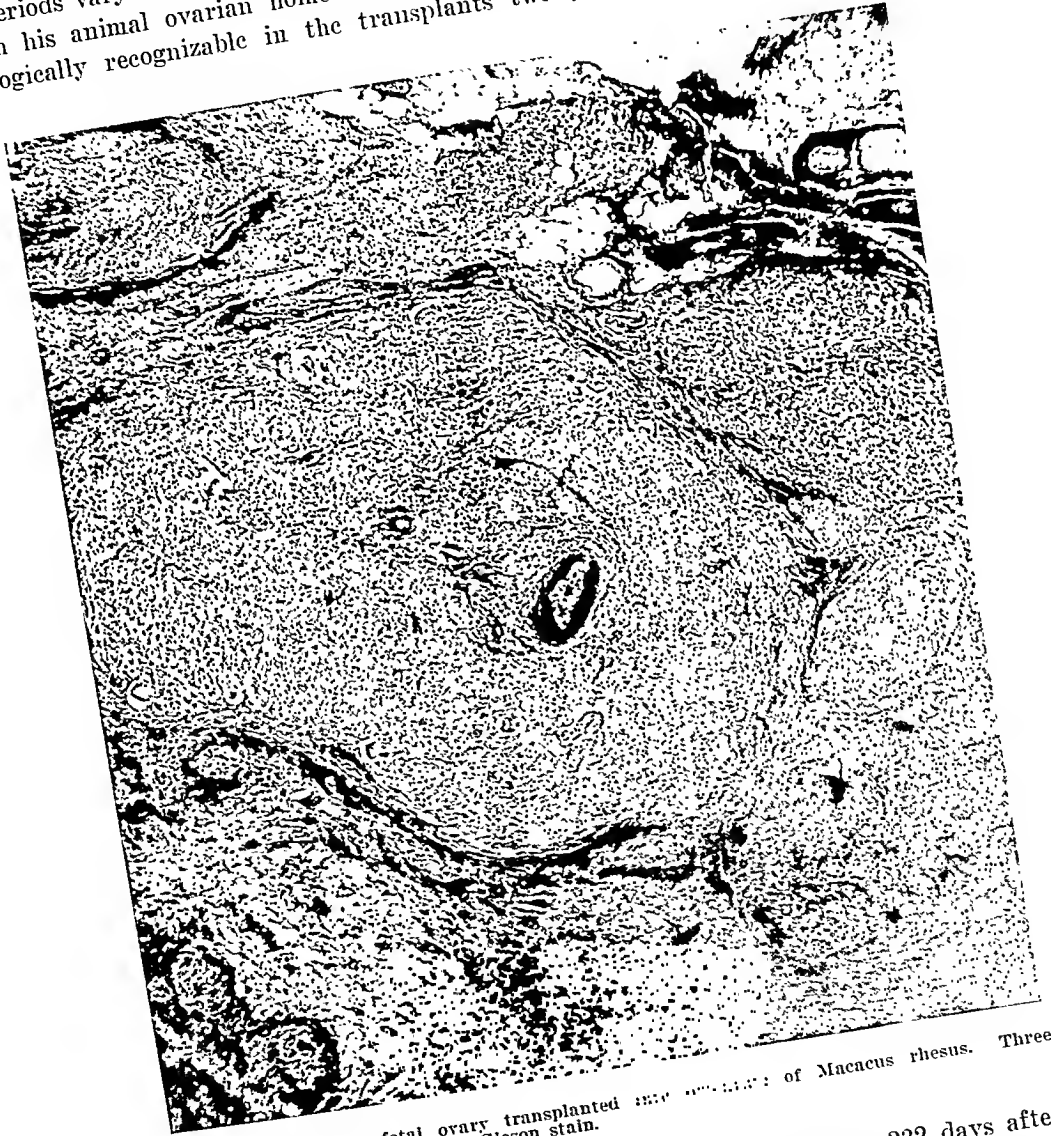


Fig. 11. Human fetal ovary transplanted into abdominal cavity of *Macacus rhesus*. Three months after implantation. Van Gieson stain.

Moore (25) found primary follicles in animal transplants 332 days after implantation, although the transplant was decreasing in size. In Lipschütz's experiments in guinea pigs he stated that 70 per cent of the cases in which the transplant "took" were functioning after nine months; that is to say, giving evidence of endocrine secretory activity and microscopic

evidence of follicular activity. In some cases more than a year and a half had elapsed.

There is, so far as I know, no case reported in the literature of an ovarian heterotransplant proved histologically to be functioning for a period even approximating eleven months after implantation.

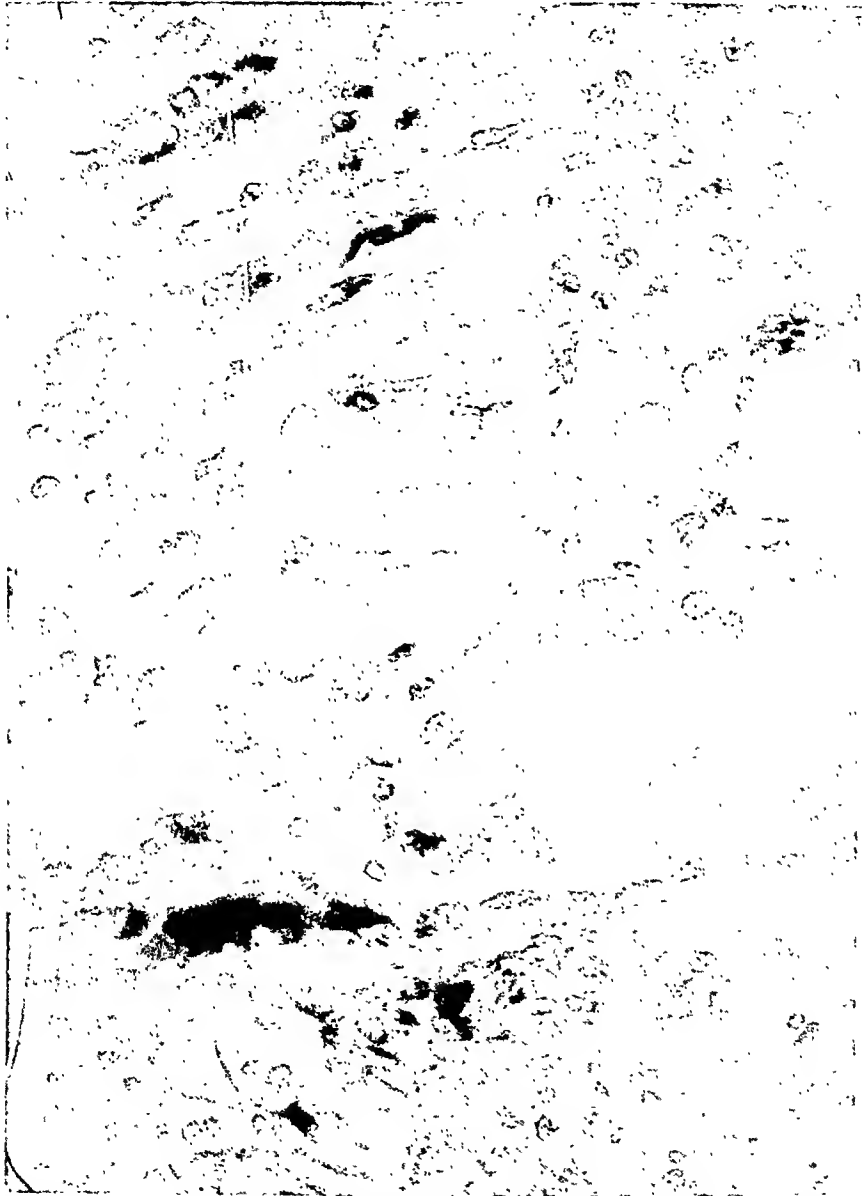


Fig. 12. Human fetal ovary transplanted into omentum of *Macacus rhesus*. Three months after implantation.

No claim is made that ovarian transplantation is of permanent value. The literature shows that after a time, perhaps a few years, the transplant will disappear, but while it survives it fulfills the functions, or at least some of them, of the endocrine secretion of the ovary. The indications for such a transplantation, whether as a prophylactic or therapeutic measure

in induced or natural menopause, are well known and I will not discuss them here. I will merely say that the proof of the possibility of successful ovarian transplantations has greatly widened the scope of practicability of this surgical procedure.

I will take the opportunity of repeating here what I have reiterated in the case of testicular transplantations, that such operations have no place as "rejuvenation" procedures, an aspect which has, unfortunately, been stressed in newspapers and to some extent in medical journals, to the detriment of surgical progress by affording opportunities to quacks and charlatans to delude and mislead the gullible public. There is no rejuvenation in the accepted sense possible by such operations, but successful testicular and ovarian transplantations do unquestionably improve the waning physical and psychic condition of patients and retard the onset of symptoms of senility. There is too much proof of this both in animals and the human subject to permit of the least doubt. From personal observation I believe the number of successes is greater in women undergoing implantation than in men.

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# THE RELATION OF WEIGHT TO DIABETES\*

HENRY J. JOHN, M.D.  
Cleveland Clinic  
CLEVELAND, OHIO

Overweight as a possible etiologic factor in diabetes has been discussed by many writers, and the present study of the weight in 528 cases was undertaken to ascertain whether or not diabetics as a rule are much overweight and the part that this condition may play in the production of the disease. The maximum weight of each patient was used in the preparation of the data presented in preference to the weight on admission, as it seemed probable that the former would serve better as an index to the rôle of overweight in the development of diabetes.

Overweight presupposes overeating, and overeating presupposes an increased demand on the insulogenic function of the pancreas, which, if it

TABLE I  
NORMAL WEIGHT CHART

Age	Boys	Girls
1	21.0	21.0
2	27.0	27.0
3	32.0	32.0
4	36.0	36.0
5	41.0	41.0
6	46.0	44.4
7	50.7	49.4
8	55.4	53.5
9	64.0	59.7
10	67.1	66.1
11	75.9	75.2
12	81.3	80.7
13	92.6	97.3
14	103.6	105.6
Height	Men	Women
4' 8"	...	112
4' 9"	...	114
4' 10"	...	116
4' 11"	...	118
5' 0"	126	120
5' 1"	128	122
5' 2"	130	124
5' 3"	133	127
5' 4"	136	131
5' 5"	140	134
5' 6"	144	138
5' 7"	148	142
5' 8"	154	146
5' 9"	159	150
5' 10"	165	154
5' 11"	170	157
6' 0"	176	161
6' 1"	181	...
6' 2"	187	...
6' 3"	192	...
6' 4"	198	...
6' 5"	203	...

is in any way subnormal, could easily be exhausted to the point of insufficiency, with the appearance of diabetes. While this reasoning is merely

\*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

clinical, without sufficient scientific evidence to substantiate the hypothesis, it offers a working basis of value to the clinician and the student in an effort to understand the evolution of diabetes. In time the further information needed may be made available, and data may be secured on the functional capacity of the pancreas before the development of diabetes and its relation to this condition. This is the goal at which we are aiming, but much more time will be required to accumulate and digest the facts.

In this study the cases of diabetes have been classified as follows: (1) by the decade in which symptoms developed, (2) by the percentage of

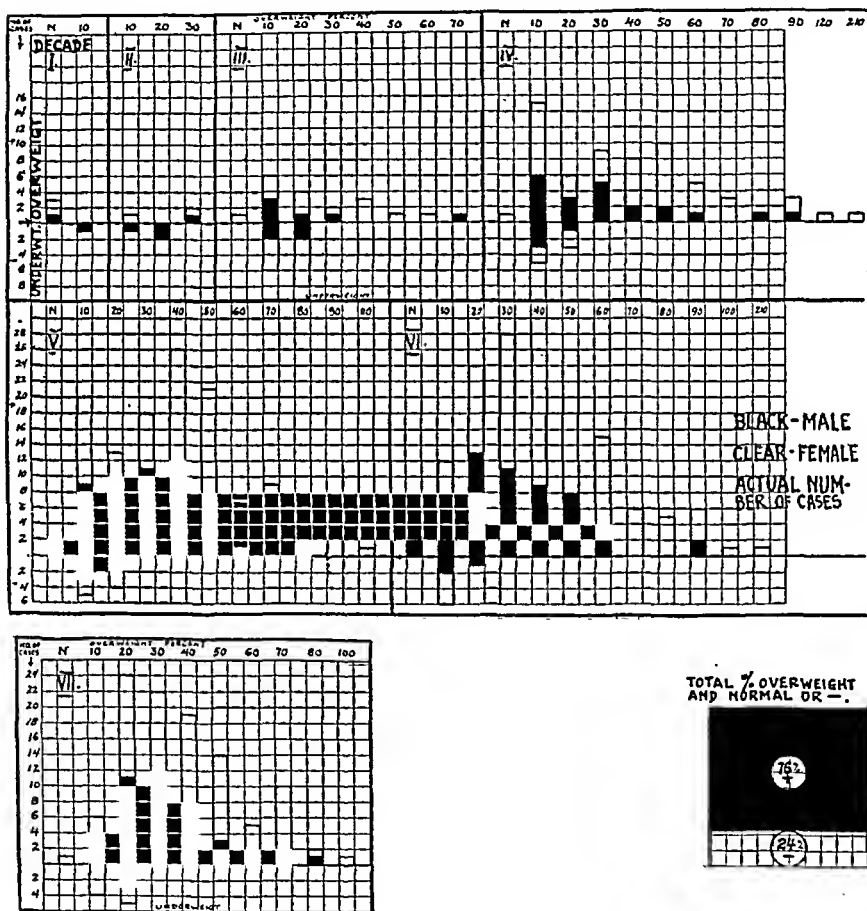


Chart 1.

over- or under-weight, (3) by sex, and (4) in comparison with a large series of normals which were furnished by Dr. F. G. Brathwaite of the Equitable Life Assurance Society of New York City. The estimations in my cases are based on the normal standards in use at the Cleveland Clinic, which are shown in Table 1.

Chart 1 shows graphically the distribution of overweight by decades in males and females. The preponderance of overweight, increasing in each



succeeding decade, is striking. The scale in the lower right-hand corner illustrates the proportion of patients who were overweight to those who were normal or underweight, all who were not more than ten per cent above normal being included with the normal. It should be noted that in three-quarters of the cases the weight was excessive, while in one-quarter it was normal or below.

Apparently the sex was without great significance as there was little difference in the results according to this classification, 72 per cent of the males examined and 81 per cent of the females being overweight.

In Chart 2 the entire series of 528 cases is analyzed to determine the percentage of overweight in the group as a whole and the relative propor-

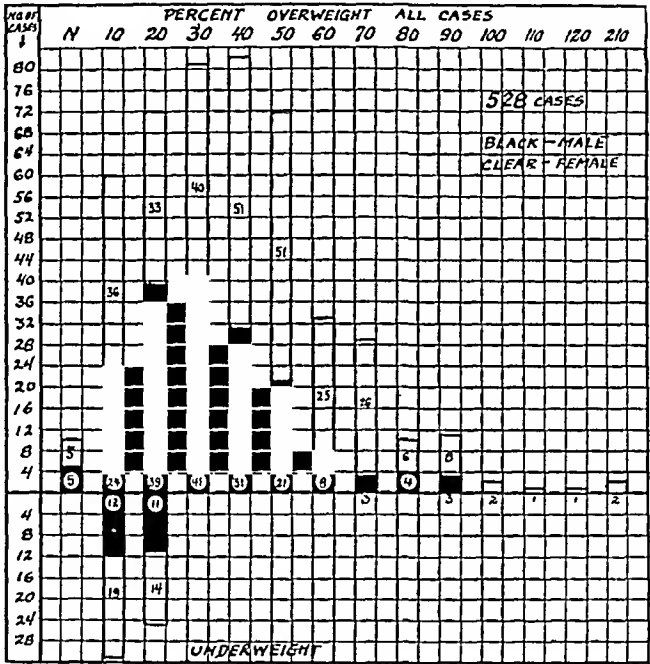


Chart 2.

tion of overweight in male and female. Again the marked preponderance of overweight is shown, running as high as 210 per cent.

In Chart 3 the entire group is analyzed by decades, regardless of sex. In the lower portion is shown the percentage in each decade of those who were underweight, normal, or not more than ten per cent above normal. In the upper portion is shown the percentage of those who were frankly overweight. Here the marked increase in overweight with each succeeding decade is graphically demonstrated, as well as the proportion between over- and under-weight.

These three charts depict the increase of weight with age in diabetic patients. In order to furnish a further basis of comparison, Dr. F. G. Brathwaite of the Equitable Life Assurance Society was requested to supply from his files the available data on the weight of non-diabetics.

Although this group does not afford a perfectly just parallel, since life-insurance statistics are based on a more or less picked class, yet it does provide a fairly satisfactory standard by which to estimate the extent of overweight in my series of diabetic cases.

In Table 2 is presented the exact information received from Dr. Brathwaite. Here only the averages in each group are shown, rather than a

TABLE II  
INCREASE IN WEIGHT IN POUNDS FOR EACH FIVE-AGE GROUP.  
DATA FROM THE EQUITABLE LIFE ASSURANCE SOCIETY, 1930.

Age Group	Aggregate Weight	Average Weight	Increase or Decrease in Weight
Men			
15-19	726170	138.9	.....
20-24	5082381	148.2	+9.3
25-29	7585199	152.6	+4.4
30-34	7254884	156.7	+4.1
35-39	5799329	160.1	+3.4
40-44	3833682	162.2	+2.1
45-49	2252252	164.4	+2.2
50-54	1225947	165.5	+1.1
55-59	596544	165.3	-0.2
60-64	189068	165.3	+0.0
65-84	43994	166.0	+0.7
Women			
15-19	570188	124.1	.....
20-24	2837446	127.9	+3.8
25-29	4084088	130.5	+2.6
30-34	3784089	133.9	+3.4
35-39	2939572	137.4	+3.5
40-44	1886537	140.7	+3.3
45-49	1161774	143.1	+2.4
50-54	662704	145.0	+1.9
55-59	289318	145.0	+0.0
60-64	82878	143.9	-1.1
65-74	15476	138.2	-5.7

TABLE III  
COMPARISON OF WEIGHT INCREASE (IN POUNDS) IN NORMAL AND  
DIABETIC SUBJECTS

Decade of Life	Equitable Life Normal Persons	Author Diabetic Patients
III.....	5.0	11.31
IV.....	3.6	45.24
V.....	2.5	45.24
VI.....	0.8	51.87
VII.....	1.5	43.81

classification of individual cases. In Table 3, therefore, my data have been reduced to a similar form, and the marked contrast between normal increase in weight and that which is found in diabetic individuals is apparent.

This same startling contrast is exhibited in Chart 4, in which Dr. Brathwaite's data on the weight of normal individuals in the third to the seventh decades are represented by the clear columns and the data on my

diabetic patients by the black columns. The height of each column represents the actual average increase in weight in pounds by decades. This is so striking that further comment would be superfluous.

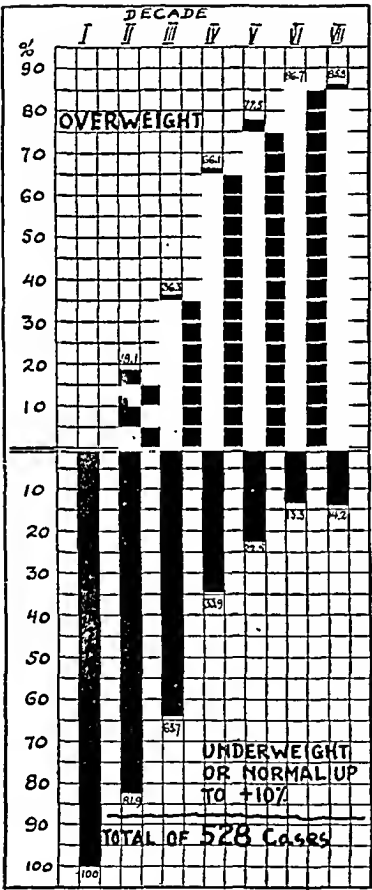


Chart 3.

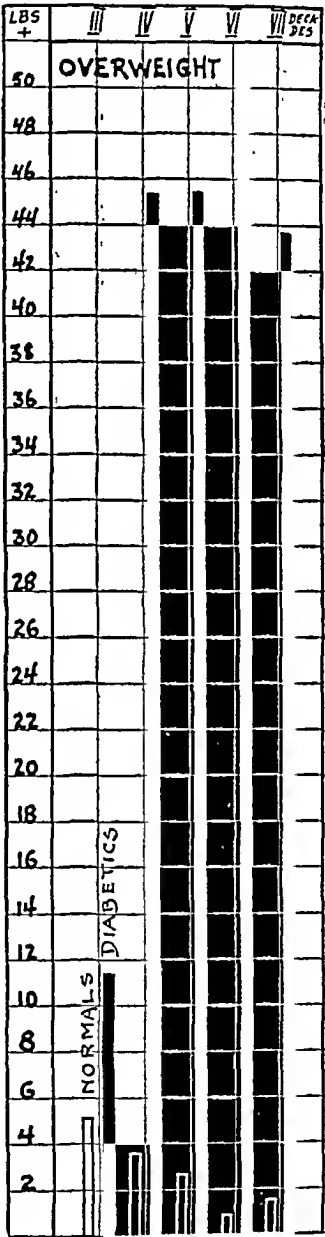


Chart 4.

CONCLUSION

Data are presented which show that diabetic patients personally studied are or have been much overweight. This is strikingly illustrated by comparison with records of a large series of non-diabetics from the files of the Equitable Life Assurance Society. The inference seems justifiable that obesity plays a rather important part in the etiology of diabetes.

The danger of obesity, therefore, should be emphasized to all patients, not only those afflicted with diabetes, for it is a factor which must be reckoned with also in myocarditis, nephritis, arteriosclerosis, apoplexy, and so forth. The public should be warned against the perils of overweight; and the place to begin is not in the office with the middle-aged patient, but in the school, where care of the health rightfully should be taught if the ideal of preventive medicine ever is to be attained.

# Book Reviews

AN OUTLINE OF ENDOCRINOLOGY. W. M. Crofton. 1929. William Wood & Company, New York. Pp. 163. 2nd Edition.

Reviewed in Arch. Int. Med. 45: 823. 1930.

THE INTERNAL SECRETIONS OF THE OVARY. A. S. Parkes, 1929. Longmans, Green and Co., Ltd., London.

Reviewed in Physiological Reviews, 14: 682. 1930.

# Abstract Department

The influence of suprarenin on the galactose assimilation of the liver (Über den Einfluss von Adrenalin auf die Galaktoseassimilation der Leber). Blösch, J., *Klin. Wchnschr.* 8: 1707. 1929.

The author describes a test for the estimation of the integrity of the liver parenchyma by the influence of adrenalin on the galactose assimilation. Forty grams of galactose was administered daily for five consecutive days, on the third of which one mgm. of suprarenin was injected subcutaneously at the same time. The galactose elimination in the urine was notably increased on this day in all or a group of ten cases exhibiting catarrhal or neosalvarsan icterus or syphilis with liver involvement. Glucose was not present. Blood sugar curves showed a marked increase in the hyperglycaemia on the suprarenin days. The possible underlying mechanism is discussed.—A. W. R.

Preliminary note on an attempt to concentrate the active principle of the adrenal cortex. Cameron, A. T. and F. D. White, *Tr. Roy. Soc. Canada (Sect. V. Biol. Se.)*, 22: 145. 1928.

From several series of experiments the following provisional conclusions are drawn. An active principle of the adrenal cortex, capable of accelerating growth when fed to young white rats, passes into solution during hydrolysis with N/10 hydrochloric acid. The action of this compound is antagonized by adrenaline. Such antagonism is overcome by simple oxidation. Methyl alcohol extraction permits concentration. Adrenaline, fed continuously to the young rat for a period of 18 days or longer, produces definite toxic effects, including marked inhibition of growth.—A. T. C.

The influence of suprarenal cortex and medulla on the growth and maturity of young (white leghorn) chicks. Eaton, A. G., W. M. Insko, G. P. Thompson and F. E. Chidester, *Am. J. Physiol.* 88: 187. 1929.

Chicks fed desiccated suprarenal medulla grew almost the same as the controls for the first few weeks, but after that time their growth was less rapid than the controls. Chicks fed desiccated suprarenal cortex grew much more slowly than the controls at first, but by the end of the first eight weeks they began to grow more rapidly and toward the end of the experiment almost equalled the controls in weight. If the weight of the testes is an indication of maturity, males receiving desiccated suprarenal cortex were more mature than either the controls or those obtaining medulla; those receiving medulla were less mature than those of the other lots.—M. B. G.

Clinical studies in suprarenal therapy. Koehler, A. E. and F. C. McLean, *Tr. A. Am. Physicians*, 44: 300. 1929.

This is a brief discussion of a preparation derived from suprarenal glands. It is a highly concentrated preparation advocated in conditions commonly attributed to suprarenal underfunction. A case of myasthenia gravis was also definitely improved by this preparation. One case of Addison's disease treated with this substance resulted in the return of the patient to his occupation for the past 18 months with complete disappearance of symptoms although stopping treatment at various times, was followed by a return of symptomatology within a week. The preliminary observations by these authors lead them to believe that this suprarenal substance has definite therapeutic value in certain cases in which suprarenal substance appears indicated.—I. B.

A caso of thymus hyperplasia (Ein Fall von Thymushyperplasie). Laband, A., *Monatschr. f. Kinderh.* 45: 225. 1929.

The clinical course in this infant of 2½ months was characterized by cyanosis, stridor, dyspnea and few rales throughout the chest. A diagnosis of pneumonia had been previously made but this was not substantiated by

either x-ray examination or post mortem findings. Death came suddenly. Post mortem examination revealed a thymus which was about one and a half times the size of the heart. The author feels that death was due to mechanical pressure on the large vessels and heart. Small hemorrhages were found in the thymus, heart and lungs.—M. B. G.

Case of hypernephroma with virilismus in a girl of 3½ years. Lundh, G., *Acta Paediat.* 9: 118. 1929.

This patient, who first showed symptoms at the age of three years, had over-developed external genitalia, a large clitoris with a hypospadiac formation and marked hypertrichosis. The uterus, vagina, urethra and hymen were normal. Post mortem examination revealed a tumor taking up the place of the left suprarenal gland. Metastases were found in both lungs. Microscopical study showed a tumor built up for the most part of large, richly protoplasmic polyhedral cells with large nuclei, often in the form of giant cells. —M. B. G.

Pathologic histology of adrenalectomized cats. MacMahon, H. E. and R. L. Zwemer, *Am. J. Path.* 5: 491. 1929.

The gross and microscopic lesions following experimental adrenal insufficiency in cats (average survival ten days) are described. Briefly, they consist in fatty degeneration of the tubules of the kidney, lymphoid hyperplasia, moderate colloid distention of the thyroid, and hyperplasia of the interstitial cells of the testis. The significance of these, and other observations on experimental adrenal insufficiency, is discussed in relation to "lipoid nephrosis," lymphoid hyperplasia and additional clinical syndromes.—Author's Summary.

The disease picture of interrenalism (*Das Krankheitsbild des Interrenalismus*). Mathias, E., *Med. Klin.* 25: 1879. 1929.

Mathias says that the loss of adrenalin does not explain the disease picture of Addison's Disease. Unfortunately, the suprarenal cortex has long been neglected. Precocious sexuality is frequent in the female with hypernephroma, less frequent in the male. One of the first symptoms noticed in hypernephroma is hairiness and a tendency to acne. Striae are also noticed. In a certain group of cases, polycythemia, hypertonicity, obesity and symptoms of Basedow's disease are present. The presence of striae in interrenalism is of significance in that the striae of pregnancy may be explained on the basis of suprarenal cortex hypertrophy present at this time. Likewise the pigmentation of pregnancy finds an analogy in interrenalism. Signs of interrenalism are also found in acromegaly. The climacterium with the tendency to beard formation, deepening of the voice, tends to show the presence of interrenalism at this time. The author pleads for further research in order to isolate the substance "interrenalin" from the cortex.—R. C. Moehlig.

A case of paroxysmal hypertension associated with suprarenal tumor. Pincoffs, M. C., *Tr. A. Am. Physicians*, 44: 295. 1929.

The patient was a married woman of 25, complaining of increasing palpitation for a period of years. The attacks were abrupt in onset, from one to three hours' duration and associated with considerable apprehension, tremulousness and nausea. Between attacks the physical examination was negative but with the onset of the symptoms the systolic blood pressure rose to 260 within a few minutes, while the diastolic pressure did not rise proportionately. The pulse during attacks rose to 110. The urine showed a constant trace of albumin. There was an intermittent glycosuria but the fasting blood sugar was normal excepting during one attack when it rose to 116 mgm. Electrocardiographic studies during the attack showed very high T waves similar to those in acute hyperthyroidism. The diagnosis of medullary tumor of the adrenal was made. Operation revealed an oval tumor of the right suprarenal gland which proved to contain adrenalin in considerable amounts. The pathological diagnosis was pheochromocytoma. Since the day of the operation the patient has never had another attack of paroxysmal hypertension; the systolic blood pressure has varied between 110 and 125 and the patient is apparently in normal health.—I. B.

The hormone of the adrenal cortex (*Über das Inkret der Nebennierenrinde*). Schmitz, E. and W. Milbradt, *Ztschr. f. d. ges. exper. Med.* 68: 393. 1929.

In previous papers the effect of extracts of the adrenal cortex were examined on pigeons with experimental beri-beri. This substance was called "cortisupren." The effect of this substance is compared with that of interrenin, the hormone isolated by Goldzieher. As first test, the authors examined the effect of both substances upon the blood fats of rabbits. They confirmed Goldzieher's observations that interrenin decreased the concentration of cholesterol and phosphorus containing lipoids, as well as that of fatty acids. The effect of cortisupren was identical, so far as cholesterol and fatty acids are concerned, but it increased the phosphatids in contradistinction to interrenin. In pigeons fed on rice the development of beri-beri is accompanied by a tremendous rise of the blood fats. If interrenin is given, the rise of cholesterol and fatty acids can be checked and that of phosphatids completely prevented. The effects of cortisupren are less distinct and negligible in relation to the phosphatids. The authors claim that cortisupren contains apparently another substance besides interrenin, which affects the phosphatids of the blood in a different way. The absence of adrenalin or choline in both preparations used could be demonstrated.—M. B. G.

The functional diagnosis of adrenal disease (*Zur Frage der funktionellen Diagnostik der Nebennieren*). Tschobokssarow, M. N. and S. J. Malkin, *Endokrinologie*, 5: 331. 1929.

The authors describe a diagnostic procedure for the definition of adrenal disease on the basis of the selective differential inhibition of "serum" and "adrenal" lipase by quinin, chloral hydrate and atoxyl. A few laboratory protocols are tabulated and two illustrative cases briefly described, in the second of which a diagnosis of hyperadrenalism is based upon the patient's response to an adrenalin test and the condition successfully treated with insulin.—A. W. R.

The hypoglycaemia of Addison's disease (*Über Hypoglykämie bei Morbus Addisonii*). Wadi, W., *Klin. Wchnschr.* 7: 2107. 1928.

The author discusses the conventional allocation of low blood pressure and blood sugar, asthenia and pigmentation to medullary insufficiency and the gastro-intestinal disturbances, delirium, convulsions, collapse, and coma to the failure of cortical function. Most of the latter are associated with the terminal phase of Addison's disease but the author contends that they arise from the hypoglycaemia and draws a parallel with the symptoms of insulin poisoning. He gives the protocol of a careful investigation on a single case. Suprarenin injection produced a notable fall in blood sugar associated with the features of a terminal condition which were relieved by glucose administration. Recurrence of the symptoms, recorded on several subsequent occasions, was always associated with low blood sugar, and except in the last and fatal attack, relieved by glucose. He concludes that the so-called "cortex symptoms," exclusive of the gastro-intestinal disturbances, are referable to the hypoglycaemia.—A. W. R.

Pneumin. A respiratory autacoid from the adrenal cortex discharged into the circulation via the lymphatics. Vincent, S. and J. H. Thompson, *J. Physiol.* 67: 3. 1929.

In decerebrate cats complete adrenalectomy performed after elimination of all anaesthetic was found to result in death from respiratory failure. Similar effects were observed when damage was done to the posterior region of the glands, and more careful investigations revealed a lymphatic plexus in this area, ligation of which caused respiratory failure. Ligation of the adrenal veins was without effect. Removal of the lymph glands into which the plexus drains, or ligation of the lymphatic trunks in the neck, brought about all the typical signs of cortical insufficiency in the decerebrate cat. Numerous and varied control experiments were made. The conclusion was reached that some autacoid, which the authors propose to call pneumin, is discharged from the adrenal body by way of the lymphatics and is essential to normal respiration in decerebrate cats. Extracts of the cortex completely restored respiration after cessation due to adrenalectomy. Experimental evidence is given to prove that the medulla is not concerned.—J. H. Thompson.



The endocrine mechanism of fever and heat regulation (*Der Endokrine Mechanismus des Fiebers und der Wärmeregulation*). Cramer, W., *Endokrinologie*, 4: 25. 1929.

An abstract of a book by the same author. Using histological evidence as a basis, the author reaches conclusions similar to those reached by physiological methods, e. g., cold stimulates excretion of adrenalin and thyroxin into the blood stream, thus maintaining body temperature. If the cold stimulus persists too long, the gland is emptied, the body temperature falls and the animal dies. The conditions of the glands are quite evident in histological sections. Gland action may be stimulated also by certain chemical substances. When such stimulation occurs in a normal animal the increased output produces fever. Fever of this type might be aseptic. Temperature regulation on the internal part of the body is thus correlated to temperature changes external to the body through the medium of the adrenal and thyroid glands. The sympathetic system is involved, of course, due to its action on sweat glands and pilomotor muscles.—B. C.

Keratoconea of endocrine origin (*Un cas de keratocone d'origine endocrinienne corrigé par l'opothérapie pluriglandulaire*). Meerhoff, W., A. Meerhoff and J. M. Pareja, *Rev. franç. d'endocrinol.* 7: 399. 1929.

This is the case of a child who had an adiposo-genital syndrome of the Babinski-Froehlich type aggravated at the same time by a bilateral keratoconea. The evolution of the glandular dystrophy and its yielding to well conducted pluriglandular opotherapy alone, without treatment of any other kind, resulted in improvement of ocular, somatic, functional, mental and cardio-vascular conditions.—J. Gagnon.

Endocrine and fatigue headaches. Stevens, N. C., *New England J. M.* 201: 801. 1929.

This paper is largely devoted to a discussion of migraine which is regarded as being of endocrine origin. It is frequently associated with a low metabolic rate and in such cases responds to thyroid by mouth. The menstrual type is sometimes ameliorated by ovarian extract over a prolonged period.—J. C. D.

Endocrine tumours. Weber, F. P., *Brit. M. J.* 1: 105. 1929.

In general, endocrine tumours may be divided into 2 groups, (1) a pathological but compensatory reaction to supply a specific hormone deficiency, and (2) true neoplasms which occur independent of any need or stimulation. Tumours of the pineal and of the interstitial cells of the testis may give rise to macrogenitosomia, while growths of the adrenal cortex, anterior pituitary, pineal or interstitial cells of the testis or ovary may produce precocious growth or precocious sexual development. Associated with nodules in the malpighian bodies of the spleen there may be anaemia, thrombocytopenia, and a tendency to haemorrhage. A number of cases are discussed.—Wm. Susman.

The regulation of metabolism. XII. The special position of carbohydrate constituents in rapidly growing cells [Embryonic and tumor cells] (*Stoffwechselregulationen. XII. Die Sonderstellung der Kohlehydratbestände in Zellen mit starker Wachstumsfähigkeit [Embryonal- und Geschwulstzellen]*). Wertheimer, E., *Arch. f. d. ges. Physiol.* 223: 619. 1929. *Abst., Physiol. Absts.* 15: 109.

When pregnant rats or guinea-pigs are rendered glycogen-free by means of cold or adrenalin, the glycogen content of the embryos and of the maternal uterus is unchanged or very little decreased. On injecting adrenalin into new-born animals (2 to 15 days old), marked stability of the glycogen stores is observed. Although the doses used were several times greater than those necessary to bring about a maximal glycogen loss in adult animals, the glycogen loss in the new-born animals was either nil or relatively small; it rose with increase in the age of the animals. Mouse carcinoma cells of Ehrlich contain only traces of glycogen or free sugar. The greater part of the total carbohydrate content (0.19 to 0.25%) is only set free after acid hydrolysis.

When the host organism is deprived of glycogen by means of cold, oxygen lack, or strychnine poisoning, or by the action of adrenaline, insulin or thyroxine, the carbohydrate content of the carcinoma cells remains unchanged. The overfeeding of these animals with carbohydrates brings about an increase in the carbohydrate content of the tissues, but not of the carcinoma cells. Similar results were obtained with rat sarcomata of Jensen. It is concluded that the carbohydrate stores of cells, which tend to multiply rapidly, are not under the control of the whole organism, and can only be metabolised by the growing cells themselves, independently of the organism.

The nature of a substance occurring in the serum of animals rendered anemic which influences corpuscular count (*Über die Natur der Blutkörperchenzahl beeinflussenden Substanz in Serum anämisierten Tiere*). Zih, A., *Endokrinologie*, 3: 81. 1929.

A substance was secured from the serum of animals which were made anemic by methods previously described and from which the spleen had also been removed, which had a marked effect on the corpuscular count. It either increased or decreased the red cell count, depending chiefly on the dosage. —B. C.

Influence of age of graft and receptor on oestrous cycle (*Influencia de la edad del animal receptor y del ovario injertado sobre el ciclo oestral de la rata blanca*). del Castillo, E. B., *Rev. Soc. argent. de biol.* 5: 271. 1929. *Abst.*, *Physiol. Absts.* 15: 119.

The grafting of an ovary from an adult rat to an adult castrate produces prolonged oestrus, interrupted by short dioestrus, then gradually dioestrus becomes longer and less regular than in normal animals. Ripe follicles and corpora lutea are found as much as 18 months after grafting. Ovaries from immature rats grafted into adult castrates produce a small number of cycles with gradually increasing dioestrus; soon dioestrus becomes permanent. Post-mortem examinations show that the graft has been completely reabsorbed. Adult ovaries grafted into immature castrates are reabsorbed; the vagina opens at the normal time, but no oestrus occurs. The most important factor is the age of the receptor organism; the age of the graft has a certain influence. Optimum conditions obtain when the graft coming from an adult is put into an adult.

Culture of mammalian testicular tissue and the nature of the interstitial tissue and interstitial cells (*Über Kulturen des Hodengewebes der Säugetiere und über die Natur des interstitiellen Hodengewebes und der Zwischenzellen*). Esaki, S., *Ztschr. mikr. anat. Forsch.* 15: 368. 1928.

From the behavior of tissue cultures of the testes of young normal and experimental cryptorchid guinea pig to vital dyes it is concluded that interstitial cells are quite distinct from resting wandering cells or histiocytes. At the periphery of the culture, the interstitial cells may change into spindle-shaped cells indistinguishable from ordinary fibroblasts. The flattened cells of the walls of the tubules are mesenchymal elements which can change into either interstitial cells or into histiocytes. Interstitial cells under favorable conditions may change into mature fibroblasts. Sertoli cells also grow out from opened tubules as spindle-shaped cells indistinguishable from fibroblasts. Some Sertoli cells change into round or polygonal phagocytic elements.—A. T. R.

Lipoid-soluble and lipoid-insoluble forms of the ovarian hormone (*Über lipidlösliche und lipoidunlösliche Formen des Ovarialhormons*). Glimm, E. and F. Wadehn, *Biochem. Ztschr.* 207: 361. 1929.

Hormone was extracted from urine of pregnancy with ether. Repeated extraction removed only about three-fourths of the active material. Remainder seemed ether-insoluble. Heating the urine with alkali increased the proportion of ether-insoluble hormone, with considerable loss of total activity. Heating with acid reversed this reaction to some extent, causing the ether-insoluble active material to become ether-soluble. Similar results obtained with purified preparations of ovarian hormone.—B. S. Walker.

Isolation of female sex hormone (Über einige Versuche zur Isolierung des weiblichen Sexhormons und über dessen Fällbarkeit mit Antimonpentachlorid). Goldhammer, H., Biochem. Ztschr. 215: 1. 1929. Abst., Physiol. Absts. 15: 118.

Placental extract in chloroform solution gives a blue color with antimony trichloride, which is characteristic for the mixture, but not for the hormone itself; antimony pentachloride precipitates the hormone itself. By treatment of this precipitate with sodium hydroxide the hormone may be isolated in an odorless and very active form from the unsaponifiable chloroform extract of the urine of pregnancy as well as from the placenta. Under certain circumstances the hormone becomes water-soluble.

Effect of ovarian hormone on sex of offspring (Bemerkungen zur experimentellen Hyperfeminisierung). Gostimirović, D. Klin. Wchnschr. 8: 2091. 1929. Abst., Physiol. Absts. 14: 663.

The results are tabulated of 55 litters from 50 mice that received "folliculin-menformon" in doses of 0.5 mouse units per day for 6 to 7 days before mating. The ratio of male and females in the litters of the controls was 1.08:1, and in the experimental animals 1.32:1.

Aschheim-Zondek's pregnancy reaction: Its significance in differential diagnosis of amenorrhea and menopausal disturbances (Die Aschheim-Zondeksche Reaktion und ihre differentialdiagnostische Bedeutung für Amenorrhoe und Klimakterium). Solms, E. and E. Klopstock, Deutsche med. Wchnschr. 55: 1919. 1929. Abst., J. A. M. A. 94: 300.

Aschheim-Zondek's pregnancy test was employed in 349 cases. The results were correct in more than 99 per cent. Further experimentation with the method convinced the authors that it is of diagnostic and therapeutic value in cases of amenorrhea and in menopausal disturbances. It has been proved that these conditions are caused either by hyperfunctioning or by hypofunctioning of the endocrine sex glands. The changes in the test animals reveal which of the two conditions is the etiological factor in each instance. In cases of hypofunctioning the therapy then supplies the missing hormones, whereas in cases of hyperfunctioning preparations that have an antagonistic effect on the hormonal secretions are administered. The authors describe four cases that show the value of this method.

Concerning the mammary gland secretion in the male. A contribution to the problem of intersexuality (Über Brustdrüsensekretion beim Manne. Ein Beitrag zum Problem der Intersexualität). Levinger, E., Ztschr. f. d. ges. Neurol. u. Psychiat. 116: 559. 1928.

Levinger reports a case of a young man, nineteen years of age, suffering with bilateral tuberculosis of the productive type. The family history revealed that the father was an alcoholic and two sisters had died of tuberculosis. The patient had suffered from the disease for six years and had suffered from bed-wetting until the age of nine years. As a child he sucked his fingers, played with dolls and loved to cook. Puberty developed normally. He had no homosexual tendencies. The physical examination revealed a very pale young man. The secondary sex characteristics were normal. The right nipple was less developed than the left and erectile contraction of the nipples was produced by mechanical irritation. The testes were normally developed, the thyroid was normal and there was marked dermatographism. X-ray examination of the sella turcica revealed that it was somewhat smaller and deeper than usual. The patient's general configuration gave one the impression of feminine characteristics. The patient had noticed that the breasts felt full and on examination pressure brought forth white fluid which showed, microscopically, colostrum. It was also noticed that there was an accessory nipple above the right nipple. Levinger then takes up in detail some of the conditions which may produce milk secretion in the male breasts. He also discusses the relationship of the different endocrine glands to development of the breasts and their function. Examining forty male individuals suffering with tuberculosis, ranging in age from eighteen to forty-five years, he found three cases of milk secretion in the male breasts. All three had true colostrum as verified by microscopic examination.—R. C. Moehlig.

The chemistry of oestrin. I. Preparation from urine and separation from an unidentified solid alcohol. Marrian, G. F., *Biochem. J.* 23: 1090. 1929. *Abst., Physiol. Absts.* 15: 117.

Urine collected 1 to 2 weeks before parturition was extracted with ether, the extract washed, and the ether evaporated. The residue was saponified with KOH and the unsaponifiable matter extracted with ether. After evaporation of the ether, the residue may be treated with a little ether or acetone, which removes the oestrin, and the saponification of this extract repeated. For large quantities of urine it was convenient to use toluene as a preservative and also to break the emulsion formed when extracting the saponified material. The solid alcohol, being only slightly soluble in ether or acetone, was left behind, and the oestrin was extracted from the final residue. When chloroform was used instead of ether, the alcohol was not obtained, but caffeine appeared in the final residue. The alcohol crystallizes in white plates, has m.p. 233° to 235°, is only slightly soluble in organic solvents and insoluble in water, is not precipitated by digitonin, does not give sterol color tests, but shows a deep brown color with acetic anhydride and  $H_2SO_4$ . It has not oestrin activity. From analysis and molecular weight determinations its formula appears to be either  $C_{26}H_{42}O_2$  or  $C_{25}H_{40}O_2$ ; it forms a diacetate, and is therefore a dihydroxy alcohol; it is saturated compound. It was not found in healthy male and non-pregnant female urine. The yield of oestrin from urine was up to 1,800 mouse units per liter of activity 0.0183 to 0.0016 mgm. per unit; the yield of the alcohol was from 0.02 to 0.2 g. per 100 liters.

The chemistry of oestrin. II. Methods of purification. Marrian, G. F., *Biochem. J.* 23: 1233. 1929. *Abst., Physiol. Absts.* 15: 117.

The unsaponifiable ether-soluble fraction obtained from urine (0.00357 mgm. M. U.) was fractionated with 70 p.c. and then 50 p.c. alcohol, without loss of activity and with definite purification; after the first treatment the unitage was 0.00167 mgm., and after the second 0.00106 mgm., the activity being in the soluble fraction. From an ethereal solution of the latter, about 2% of the activity was extracted by 4.8 p.c. KOH, the resulting unitage being 0.000135 mgm.; part of the activity remained in the fractionation. Oestrin is stable to boiling aqueous alkali and sodium chloride, but is destroyed by ether peroxides. It can be extracted by ether from neutral or acid aqueous solution completely, from alkaline solution only incompletely. If an alkaline solution has  $CO_2$  bubbled through it, ethereal extraction becomes complete. The purest fraction was soluble in lower alcohols, acetone, ethyl acetate, and chloroform; slightly soluble in ether, benzene, hexone, 30 p.c. alcohol, and water. On diluting an alcoholic solution with water and evaporating off the alcohol, two-thirds of the activity was precipitated.

Temporary sterility of the wife following the hypodermic injection of sperm from the husband (Sur la question de la stérilité temporaire de la femme a la suite de l'injection hypodermique de sperme du mari). Naiditch, M. S. and Mme. N. A. Zaitseva-Kalinovskaya, *Russian J. Endocrinol.* 3: 140. 1929.

The authors have not been able to cause temporary sterility in the wife by subcutaneous injection of sperm of the husband, and do not recommend the method because of the difficulty of obtaining living spermatozoa in a sterile state. For the production of spermotoxins, the use of human spermatozoa presents no advantages over the use of animal spermatozoa.—M. O. L.

Anterior pituitary-implantation in Rhesus (*Hypophyssen-orderlappen-implantation in Rhesusaffen*). Ehrhardt, K., H. Weisbader and L. Foesaneanu, *Endokrinologie*, 3: 401. 1929.

Two Rhesus monkeys, observed for 6 months, showed regular menstrual periods. One ovary was removed from each and examined macro- and microscopically. No sign of corpus luteum was found. Pituitary implants were then made. This was followed by an enlargement of the uterus and the usual livid coloring. The second ovary was removed and examined, but corpus luteum was not found. These authors suggest the use of these animals in studying the effect of the pituitary hormone upon the follicular part of the ovary.—B. C.

The effect of daily transplants of the anterior lobe from gonadectomized rats on immature test animals. Engle, E. T., *Am. J. Physiol.* 88: 101. 1929.

Experiments were conducted on 62 rats of both sexes, one group being gonadectomized at the age of 20-30 days and the second at one year of age. The animals were sacrificed eight months after the operation and their pituitaries transplanted on successive days into immature mice and rats. A control group received the glands from normal non-gonadectomized rats. Results indicate that the anterior lobe of rats which have been gonadectomized for eight months contain a greater supply of gonadal stimulating hormone than occurs in the normal animal. This is shown by the earlier sex maturation and increased size of the ovaries of the test animals receiving transplants from the castrated animals. This would seem to indicate that the anterior lobe continues to elaborate gonad stimulating hormone even after castration. There is no sex difference in the biological potency of the gland of gonadectomized donors and no significant difference as regards the age of the donor at the time of gonadectomy.—M. B. G.

Does cerebro-spinal fluid contain anterior lobe pituitary hormone (Liquor und Hypophysen-vorderlappenreaktion)? Erhardt, K., *Klin. Wchnschr.* 8: 2330. 1929. *Abst., Physiol. Absts.* 15: 48.

Using the Zondek-Aschheim reaction, the cerebro-spinal fluid obtained by lumbar or suboccipital puncture was tested for the presence of the active principle of the anterior lobe of the pituitary. Neither from normal children, adults nor from cases of disease of the gland was a positive reaction obtained. In pregnancy the reaction was also negative.

Pituitary implantation and sexual stimulation in toads (*Implantación de la hipófisis y estimulación sexual en el sapo*). Houssay, B. A. and J. M. Lascano-Gonzalez, *Rev. Soc. argent. biol.* 5: 397. 1929. *Abst., Physiol. Absts.* 15: 116.

Subcutaneous implantation of the glandular lobe of the pituitary produces (a) in males stimulation of the testicles, as seen by increase in weight and spermatogenesis, and of the central nervous system, as seen by copulatory embracing out of season; (b) in females, ovulation with expulsion of eggs. This effect is only obtained with toad pituitary; it is not obtained with the pituitary of mammals, birds, snakes, and frogs, nor with pregnant women's urine. The active principle is destroyed by heating, and is insoluble in alcohol and acetone. The anterior pituitary conditions the growth and maintenance of the gonads, and therefore the secondary sexual characters.

Pituitary tumor with goiter and acromegaly. Ironside, R., *Proc. Roy. Soc. Med.* 23; 6. 1929. (*Sect. Neur.*)

The patient was a woman of 60 who, 25 years before, began to take larger shoes and gloves and to notice a swelling of the neck. An operation had been performed 15 years before for substernal goiter on account of dyspnea. This had resulted in residual paralysis of the left recurrent laryngeal nerve. The patient now presented distinct evidences of acromegaly with headache, hypertrophic changes in the joints of the limbs, enlargement of the sella turcica, and enlargement of the supraclavicular lymphatics and of the submaxillary glands. There were characteristic alterations in the fields of vision, hemorrhages in both fundi, and arterial hypertension.—I. B.

Acromegalic diabetes (*Le diabète acroméganique*). Martin, E., *Rev. méd. de la Suisse Romande*, 49: 693. 1929.

Pituitary patients often have difficulties in sugar metabolism. Acromegalic diabetes is not completely explained either by the hyperglycemic action of the pituitary hormone or by a tumoral compression of the infundibular nerve centres, but is more probably explained by the neurocrinic effect of a hypophysis in hyperfunction associated with changes of the endocrine pancreas. The "neurocrine" seems to be a type of secretion of great interest since it explains the histo-physiological correlations of an endocrine gland and the sympathetic system. In certain cases of diabetes if the pancreas is the principal cause of

the illness the changes in the other endocrine glands cause us to speak of pluriglandular diabetes. These cases help us in understanding acromegalic diabetes and the role and interdependence of the endocrin-sympathetic system in the equilibrium of the sugars.—J. Gagnon.

The possibility of estimating the size of the sella turcica (Über die Möglichkeit einer objektiven Grossenbestimmung der Sella Turcica). Sartorius, W. Monatschr. f. Kinderh. 45: 259. 1929.

The author studied the size of the sella turcica in 100 normal children between the ages of 1 and 10 years and presents a curve which demonstrates an increase in the size of the sella turcica in direct proportion with the age. No reference is made to previous American work on this subject.

—M. B. G.

Investigations of the functions of the anterior lobe of the hypophysis: the influence of extracts of the anterior lobe upon the genital apparatus and flow of milk in the rabbit (Recherches expérimentales sur les fonctions du lobe antérieur de l'hypophyse: influence des extraits du lobe antérieur sur l'appareil génital de la lapine et sur la montée lacteuse). Stricker, P. and F. Grueter, Presse méd. 37: 1268. 1929.

Aqueous extracts were prepared from anterior pituitaries and injected into female rabbits, (1) immature, (2) virgin adults, (3) spayed adults, (4) pregnant, (5) pseudo-pregnant. Immature rabbits were given injections of aqueous extract equivalent to 0.5 gm. of anterior pituitary. Second injections were given 24 or 48 hours later. On the fourth or fifth day the ovaries were greatly enlarged and congested. There was enlargement of follicles with hemorrhage in some and even formation of corpora lutea in some. If a series of 6 to 12 injections was given the reaction was intense and the ovaries resembled a bunch of grapes. There were then found ripe follicles, atretic follicles, hemorrhagic follicles and corpora lutea in various stages of development. The uterine horns were enlarged and congested and sections showed the lutein phase in which the mucosa is prepared for the nidation of the ova. In normal adult females after 4 to 8 injections of extract, equivalent to 1 gm. or 1.5 gm. of anterior lobe in each dose, the ovaries were found to contain as many as 30 corpora lutea and 15 to 20 hemorrhagic follicles. The uterine horns were greatly thickened. Rupture of follicles in rabbits in heat was brought about by one injection of anterior pituitary extract in the absence of coitus. Ovariectomized adults reacted differently than normal females to injections of anterior pituitary extract. The uterine horns were congested but the mucosa did not show the changes essential for nidation of the ova. The mammary glands, however, were influenced by the injections. Normal adult females in heat were mated with males which had been rendered improcreant by vasoligation. On the 10th day after the infertile coitus the development of the uterus, corpora lutea and mammary glands had reached the maximum. Extract of anterior pituitary was then injected 4 or 5 times. On the 18th or 20th day the animal was killed and the ovaries were found to be extremely congested and filled with atretic follicles, hemorrhagic follicles and corpora lutea, 25 to 45 per ovary. The uterine mucosa had not been allowed to return to the resting stage but had remained in the stage of proliferation ready for nidation of ova. There was also an abundant secretion of milk from the mammary glands although the animals were not pregnant. Immature rabbits (6-8 weeks old, weighing 900-1200 gm.) were given 4 to 6 injections of an aqueous extract of anterior pituitary. Each dose corresponded to 1 gm. to 1.5 gm. of fresh gland. The ovaries were found to contain mature follicles, hemorrhagic follicles and corpora lutea but the mammary glands did not show any appreciable change. It seems possible then that the mammary gland can react to anterior pituitary hormone only when it has been influenced by some specific substance which is found only in an adult animal. This specific substance may be the hormone of the corpus luteum. Rabbits in heat were submitted to infertile coitus and 8 to 10 days later were given 2 or 3 injections of anterior pituitary extract. In 2 to 4 days after the first injection a flow of milk began. When the injections were continued for 7 to 8 days the mammary glands became engorged with milk. It is possible that the mammary gland secretion was conditioned by the intense activity of the ovaries. In order to rule out this factor another experiment was performed in which rabbits were ovariectomized on the 10th day after infertile

coitus. Injections of anterior pituitary were started on the day of operation or the following day. The flow of milk occurred 2 or 3 days after the first injection and became very abundant by the 6th to 10th day if the injections were continued. There was no effect on the genital tract and the uterine horns showed castration atrophy. In one rabbit, ovariectomized after infertile coitus, the mammary glands were allowed to atrophy for 3 months. Upon injecting anterior pituitary extract the mammary glands became active again and secreted milk. No success was had in provoking the flow of milk in ovariectomized rabbits unless there had been either fertile or infertile coitus previous to the injections of extracts of anterior pituitary. Injections of folliculin in addition did not alter this finding. In pregnant animals injections of anterior pituitary extracts caused a flow of milk but also caused abortion. In only one experiment secretion of milk took place without the death of the fetus. In a normal female which had nursed her young and weaned them and had been without milk for two weeks, the flow of milk was started up again by a single injection of anterior pituitary extract. A dog under quite similar conditions was able to nurse two adopted puppies for several days.—E. P. Bugbee.

Effects of feeding silkworms on extracts of the anterior lobe of the pituitary gland. Thompson, J. H., Arch. f. Entwicklungsmechn. d. Organ. 114: 578. 1928-29.

Feeding silkworms on fresh lettuce leaves soaked in an extract of the anterior lobe of the pituitary (Parke, Davis & Co.) caused marked retardation in growth, delayed metamorphosis and increased the mortality at the various stages of metamorphosis. Not a single experimental animal reached the complete chrysalis stage. The circulation was slowed. The author believes that these effects are due to a failure of metabolism, especially of carbohydrates. —A. T. R.

Carbohydrate metabolism in acromegaly. Wishnofsky, M. and C. S. Byron, J. Lab. & Clin. Med. 15: 216. 1929.

The disturbance in carbohydrate metabolism in acromegaly may be incidental to or concomitant with diabetes mellitus. Of cardinal importance is the fact that although pituitrin neutralizes the effect of insulin on blood sugar concentration, it does not affect the action of insulin on the oxidation mechanism of glucose. This fact may be utilized in determining the nature of the carbohydrate disturbance. If after the administration of a large quantity of glucose the respiratory quotient fails to approach 1, diabetes mellitus is present; if the respiratory quotient does approach unity, the glycosuria is symptomatic regardless of its degree.—I. B.

Further investigations upon the preparation, biological actions and clinical uses of Prolan, the hormone of the anterior lobe of the hypophysis (Weitere Untersuchungen zur Darstellung, Biologie und Klinik des Hypophysenvorderlappenhormons [Prolan]). Zondek, B., Klin. Wchnschr. 8: 157. 1929.

Zondek details further investigations made by himself and Aschheim on the effect of the hormone of the anterior lobe of the pituitary gland ("Prolan") on the genital apparatus. In contrast to the ovarian hormone it is destroyed by heat, strong acids and alkalis, while it is insoluble in most solutions which dissolve lipoids. Previously biological tests have been confined to mice and rats, but the author has now used guinea-pigs. "Prolan," 2 to 4 cc., equivalent to 60 to 120 rat units, was injected for 10 to 14 days and caused considerable changes in the sexual organs. The uteri increased in size from thin tubes to the thickness of a finger, became livid blue in color and gave the appearance of early pregnancy. The ovaries increased in size to that of a cherry stone and showed multiple haemorrhagic areas with corpora lutea. Microscopical examination of the uterine mucosa revealed hypertrophy similar to the changes during pregnancy. The ovaries manifested luteinization with hindrance of ripening of the follicles. Eventually "Prolan" was concentrated so as to contain 30 rat units per cc. and 60 units was considered to be the minimum dose for human beings. The author has found that the injection of 3 cc. is followed by a definite increase in cholesterol in the blood. When it is injected intramuscularly, hyperaemia of the genital tract occurs as in pregnancy. The temperature of the pelvic organs varies from 0.5° to 1° C. higher

than that taken in the axilla. Possibly this effect may prove of value in the treatment of inflammatory conditions of the pelvis. If "Prolan" be injected from the first day of menstruation and continued until the eighth day of the cycle, microscopical examination of the uterine mucosa reveals changes equivalent to those found usually from the fourteenth to sixteenth days. Changes in the ovaries have been observed, but the connection with the injections has not yet been established. While in two instances milk secretion was provoked, this was not found to occur in the majority of cases. Ten patients with amenorrhoea due to glandular deficiency have been treated. In two instances after daily injections for six days and following on an interval of a week, curettage revealed a mucosa with prolific glandular formation and commencing secretion. In five patients menstruation began from seventeen to thirty days after injections and recurred in three to four weeks. Further work remains to be done to determine the dosage and length of administration to insure a permanent rhythm. The author's results with oral administration are not satisfactory and may be due to the smallness of the dose or the destruction of the hormone in the stomach and intestines. While with the rat the oral route is successful, this is not so with mice, even in larger doses.—E. P. Bugbee.

The diagnosis of pregnancy by the demonstration of the hormone of the anterior lobe of the pituitary in the urine (*Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons*). Aschheim, S. and B. Zondek, *Klin. Wchnschr.* 7: 1404. 1928.

In previous work Aschheim and Zondek pointed out the physiologic action of the anterior lobe hormone of the pituitary upon the development of the ovary of the infantile white mouse. They have observed three reactions: (1) Ripening of follicles, ovulation, and oestrus; (2) "blood spots" (hemorrhagic follicles); (3) luteinization of follicles and formation of corpora lutea atretica. These reactions could be provoked only by the anterior lobe of the hypophysis from either sex and the authors conclude that this hormone is the one specific sex hormone. They found also that this hormone is stored in the decidua, placenta and corpus luteum of pregnancy as these substances when introduced into test mice produced the above-mentioned anterior lobe reactions. Further investigations showed this hormone to be present in the blood serum and urine of pregnant women, the urine containing the larger amount of the active principle. Subcutaneous injections of small doses of urine produced the characteristic changes in the ovaries of the test mice. Since urines of non-pregnant individuals caused no reaction the authors conclude that this forms a reliable means for the diagnosis of pregnancy. For this test the authors use at least 5 infantile female mice 3-4 weeks old and weighing 6-8 grams. The morning urine is most desirable since it contains the hormone in greatest concentration. Six injections are given in the course of three days, the dosage ranging from 0.2-0.4 cc. At the end of 100 hours the mice are autopsied and the reaction of the ovaries observed. In the majority of instances a correct diagnosis could be made macroscopically but whenever the reaction was doubtful a microscopic tissue examination was necessary. A definite positive reaction is easily recognized by the presence of "blood spots" but a negative reaction must always be checked microscopically. Enlargements of the uterine horns and the presence of a positive Allen test (changes in the vaginal mucous membrane indicating oestrus) are due to the presence of ovarian hormone and are not diagnostic of pregnancy. The ovarian hormone results either secondarily to the action of the anterior lobe hormone upon the mouse ovary or has been introduced directly with the urine. Reactions 2 and 3 are essential to the diagnosis of pregnancy, i.e., formation of "blood spots," luteinization of follicle epithelium and the development of corpora lutea atretica. The presence of one hemorrhagic follicle, one luteinized follicle or one corpus luteum atreticum suffices for the positive diagnosis. The anterior lobe hormone was found in greatest amounts during the early months of pregnancy and gradually decreased in amount as pregnancy approached full term and disappeared after the first few days of the puerperium.—H. C. Mack.

The influence of insulin and epinephrin on glycogen formation in the liver. Cori, C. F. and Gerty T. Cori, *J. Biol. Chem.* 85: 275. 1929.

Deposition of liver glycogen during a continuous intravenous injection of a large excess of glucose was determined in nephrectomized rats under amyral



anesthesia. For an equal quantity of glucose injected, the insulinized animals showed a blood sugar level and a glycogen content of the liver approximately one-half of that of the control animals. When a similar blood sugar level was maintained in control and insulinized animals by injecting less glucose into the former than into the latter, there was no difference in the amount of glycogen deposited in the liver of the two groups of animals. It was concluded that the blood sugar concentration is a factor determining the rate of glycogen formation in the liver. When epinephrine was injected, less glycogen was formed than in the control animals receiving the same amount of glucose, in spite of the fact that the blood sugar level of the former animals was nearly twice as high as that of the latter. The low glycogen content of the liver was ascribed to a preponderance of mobilization over new formation of live glycogen in anesthetized animals receiving epinephrine injections.—Authors' Abst.

**Duration of anticoagulant action of heparin in vivo in relation to dosage.** Gross, P., *Proc. Soc. Exper. Biol. & Med.*, 26: 383. 1929.

The intravenous injection of heparin is followed by an immediate increase in clotting time. The rate of return toward the normal clotting time is very rapid for one-third of the duration of the heparin action, and subsequently, more slowly. In general, there is an approximate relationship, as expressed by a graph, between the dose of heparin per kgm. of body weight and the duration of the heparin effect in rabbits.—M. O. L.

**Diabetes with hypertrophy of the cortex of the suprarenals.** Chiari, H., *Wien. klin. Wchnschr.* 42: 1318. 1929.

A man, 54 years old, with diabetes, died in coma, despite the use of 100 units of insulin with 40 grams of glucose intravenously. Necropsy showed gangrenous pneumonia of the upper lobe of the left lung, certain atrophic changes in the pancreas, and marked hypertrophy of the suprarenal cortex. The suprarenal glands weighed 20 grams each, and the cortex measured four to five millimeters in thickness. The enlargement was not the result of adenomatous growths. Microscopically, there was a marked diminution of fatty substance in the cortical cells. The author discusses various facts and theories concerning the relationship between the changes in the cortex of the adrenals and those in the pancreas and the effect of the former on blood sugar, but was unable to come to a satisfactory conclusion.—H. Ulrich.

**Hyperglycemia following the portal injection of insulin.** Collens, W. S. and J. R. Murlin, *Proc. Soc. Exper. Biol. & Med.* 26: 485. 1929.

There was a transient rise in blood sugar obtained five minutes following the portal injection of insulin. The dose of insulin employed was .05 and 0.1 unit per kilo of body weight. The results seem to indicate that one of the functions of insulin, if given in large enough dosage, is a glycogenolytic one.—W. S. Collens.

**Diabetes in the tuberculous.** Crow, S. L., *Southern M. J.* 22: 1079. 1929.

Six cases are described. The author concludes: (1) Tuberculosis is probably no more frequent in diabetics than in non-diabetics. (2) When these two diseases co-exist, tuberculosis is usually the complication. (3) Best results are obtained when diabetes is given first importance; therefore maintenance of a normal glycemia is the ideal goal of treatment. (4) As a result of the better management of diabetics, the prognosis of cases complicated with tuberculosis has been greatly improved.—J. C. D.

**Diabetic coma—then and now.** Fitz, R., *New England J. M.* 202: 967. 1929.

This paper gives specific rules for meeting this condition and a study of cases. Coma is preventable in most cases, can be treated with excellent prospects by insulin, and does not represent necessarily a terminal condition.—J. C. D.

Studies in carbohydrate metabolism. VI. The antagonistic action of pituitrin and adrenaline upon carbohydrate metabolism, with special reference to the gaseous exchange, the inorganic blood phosphate and the blood sugar. Lambie, C. G. and F. A. Redhead, *Biochem. J.* 23: 608. 1929. *Abst., Physiol. Absts.* 14: 650.

One cc. pituitrin subcutaneously in man postpones the rise in metabolism produced by injecting intravenously 20 g. glucose or dihydroxyacetone; the increase is greater with the latter than with glucose, and occurs earlier; pituitrin delays its maximum without postponing the onset, as in the case of glucose. The rise in metabolism produced by 10 to 15 units of insulin is usually abolished by 1 cc. pituitrin, which alone usually decreases the metabolism, although raising the respiratory quotient. Pituitrin raises the blood sugar and counteracts the fall due to insulin, but usually causes a fall in blood inorganic P. The effects of adrenalin are in certain respects similar to those produced by pituitrin, but it increases metabolism, and dextrose and adrenalin together produce an additive effect on the metabolism. In the rabbit the rise of blood sugar produced by injecting dextrose is increased by giving pituitrin simultaneously. Pituitrin raises the blood inorganic P, but dextrose and dihydroxyacetone reduce it; large doses of pituitrin counteract the fall due to the latter, but have less effect on that due to dextrose. It is considered that the effects of pituitrin and adrenalin upon metabolism may be due to alterations in the blood distribution in the body and to increased work of the heart or intestinal muscle, and that it is unnecessary to postulate a direct antagonism between insulin and pituitrin or adrenalin.

Pathogenesis and treatment of endocrine dermatoses in women. Samuel, M. and L. Strauss, *Med. Klin.* 25: 1698. 1929.

Employing a modified Bang's micro-method and, in a few instances, checking the results by the method of Hagedorn-Jensen, the authors made fasting blood sugar determinations on 250 cases of pruritus and related dermatoses in women and 40 cases of the type which belong to the domain of ovarian and similar disturbances. In the light of previous work and their own, they have been struck with the apparently very definite association between such diseases and disturbances in carbohydrate metabolism. As a result of the studies in their cases they were led to recognize the occurrence of a form of very slight hyperglycemia, more or less fleeting in character, which appears in otherwise healthy women and girls in the course of pruritic diseases and disturbances in ovarian function. Among the pruritic dermatoses studied they mention pruritus vulvae, with and without disturbances of vaginal secretion, general pruritus, dermatitides, intertriginous eczema of the vulva and anal eczema. Of the 250 cases belonging to this group two-thirds were women in the climacterium and pre-climacterium, and among the remainder of those studied the married women were much in excess of the unmarried. Those women who had borne children constituted the chief contingent with blood sugar increase. Of the 250 pruritus cases 164 showed a more or less marked increase of fasting blood sugar with values ranging from 125 mgm. per cent to 165 mgm. per cent. The pruritus cases at the climacterium showed the greatest incidence of hyperglycemia, with blood sugar values on the average higher than in the young women and girls. As illustrative of the pruritic type of case studied, the authors briefly cite three cases of patients, one, aged 48 with pruritus vulvae, a second, aged 42, preclimacteric, with pruritus, and a third, aged 32, with burning in the vagina and an intensely itching intertriginous eczema. No improvement had resulted in any of the cases under ordinary treatment. The fasting blood sugars in the three cases were, respectively, 156 mgm. per cent, 138 mgm. per cent and 148 mgm. per cent. Treatment in the first instance with a diabetic diet was of no avail. All the cases responded favorably almost immediately after a daily single injection of insulin ranging from 10 to 15 units over periods of 5 to 8 days and thereafter every second day for one or two weeks. This treatment was augmented with a light anti-diabetic diet. In the third case cited the blood sugar fell to 122 mgm. per cent two months after the treatment. About one-half of the women with disturbances of ovarian function and related manifestations showed more or less gross disturbances in carbohydrate metabolism. Hyperglycemia was prominent at the climacterium and also in younger women with menorrhagia and painful menstruation of ovarian dysfunction. Treatment with insulin in these cases resulted in less menstrual bleeding and much subjective relief. The

authors in this connection mention the fact that an increase of blood sugar level has been relatively frequently observed during menstruation and pregnancy, phenomena which would serve to support the assumption that the findings and results in their present group of cases are to be explained on the basis of endocrine interrelationships. They conclude that all these findings point with reasonable certainty toward endocrine relationships between the ovary and carbohydrate metabolism. Samuel and Strauss esteem the practical aspect, as well as a diagnostic support, of their investigations to be the average good effect of small doses of insulin in the diseases under consideration. They claim to have observed even a favorable influence of insulin in cases of pruritus and related dermatoses and also in ovarian dysfunctions, in which the blood sugar was not increased. By their experience, ordinarily, a daily 10 to 15 unit dose of insulin for a few days to a period of 14 days, with a relatively poor carbohydrate diet, suffices to effect the disappearance of the disease manifestations.—M. H. Goodman.

**Synthalin-B in diabetes mellitus.** Ulrich, H., *New England J. M.* 202: 814. 1929.

This drug, a modified synthalin (deca-methylin-diaguanidin), was given by mouth in seven uncomplicated cases of diabetes. There was definite reduction of blood sugar in all cases, unpleasant or toxic symptoms in three. This drug may supplement insulin in certain cases but must be used with caution until its toxic properties are better understood.—J. C. D.

**Concerning certain factors which may influence the sugar content of the blood and urine.** Watson, E. M., *J. Lab. & Clin. Med.* 23: 234. 1929.

The relation between the blood sugar concentration, the hourly output of sugar in the urine, and the reaction of the urine was studied in a series of non-diabetic and in a series of diabetic patients on a standard diet. There appeared to be no constant relationship between the reaction of the urine and the sugar content of the blood and urine except perhaps during the morning. When breakfast was omitted, an increase in the output of sugar in the urine occurred, and in the case of diabetic individuals, there was an obvious rise in the blood sugar as well. This increment accompanied an increase in the alkalinity of the urine. Since the morning alkaline tide of the urine appears to be related to an alteration in the acid-base balance associated with the change from the sleeping to the waking state, the authors suggest that the same process of readjustment may be the factor in causing an increase of the blood and urine sugar during the early part of the day.—I. B.

**The clinical syndrome of hyperparathyroidism.** Barr, D. P. and H. A. Bulger, *Tr. A. Am. Physicians*, 44: 238. 1929.

This is a brief discourse on parathyroid hyperactivity with two illustrative cases. Clinical hyperparathyroidism, a condition resembling the overdosage of parathormone in animals, is associated with hypercalcemia, excessive excretion of calcium in the urine, hypotonia of muscles and a tendency to metastatic calcification. This state occurs most frequently in association with generalized von Recklinghausen's disease, of which it may possibly be the cause. It may occur also as a secondary manifestation in a variety of conditions among which must be included multiple myeloma, a case of which has been reported.—I. B.

**The action of parathormone in tetany due to parathyroid extirpation (Die Wirkung des Parathormons bei Tetania parathyreopriva).** Elmer, A. W. and M. Schefs, *Klin. Wehnschr.* 8: 1404. 1929.

The authors report four cases of tetany following thyroidectomies, treated with parathormone. On comparing the action with calcium preparations and vigantol in these cases, they found that the parathormone was more efficacious and acted with decidedly greater promptness. The dosage varied with the individual case, controlled by blood calcium determinations. Concomitant with the clinical improvement, blood chemistry changes occurred. The phosphorus and blood potassium were lowered. The influence upon the alkali reserve and the coagulation time was not constant. It is recommended that parathormone be used in all cases, especially the acute cases with severe symptoms. In chronic cases, simultaneous peroral calcium administration is advised.—O. O. Meyer.

**Hyperparathyroidism (hyperfunction of a parathyroid tumor in a case of generalized osteitis fibrosa).** Hunter, D., *Proc. Roy. Soc. Med.* 23: 27. 1929. (Sect. Med.).

The patient was a single woman of 41 complaining of pain in the right knee on climbing stairs. The joint was not swollen. Soon there occurred pain in the lower part of the back and the entire left leg. Within 2 years after the onset she was unable to walk without assistance due to pain in the lower spine and right knee. Shortly afterward there occurred a sharp attack of right lumbar pain, increased frequency of micturition and vomiting which subsided within a week. The family history was not significant. Physical examination and a clinical study including radiograms yielded a diagnosis of hyperparathyroidism. The excretion of calcium was found to be equivalent to the continuous administration of about 120 units of parathormone daily. A suspected parathyroid adenoma resulted in operation. It was found that the left inferior parathyroid gland was replaced by a cystic adenoma and this was excised. Two days after the removal of the tumor the calcium and inorganic phosphorus values of the blood were restored almost to normal, and by the fourth day pressure on the bones no longer caused pain. The author concluded that the tumor served as a hyperfunctioning ductless gland which was the primary cause of the bone disease.—I. B.

**Pineal syndrome (ocular palsies and precocity) in a boy of 12.** Adie, W. J., *Proc. Roy. Soc. Med.* 23: 2. 1929. (Sect. Neur.)

The patient was a boy aged 12 who complained of headache, "fits," double vision, and shaking of the right arm, all of one year's duration. Nothing was known of his early history except that at the age of 8 he was "fully developed" and was not permitted to undress before his sisters. His sexual development was that of a young adult. He was intelligent but not precocious in book-learning. He was also an incorrigible thief. He presented, among others, the following signs: Left pupil almost inactive to light; both pupils very sluggish on convergence; upward movements of eyeballs absent; downward movements poor; convergence very poor; coarse tremor of right arm of intention type, and internal hydrocephalus.—I. B.

**The treatment of bovine tuberculosis by extracts of spleen (Essai du traitement de la tuberculose, chez les bovidés, par les extraits spléniques).** Biélinisky, A. D., *Russian J. Endokrinol.* 3: 136. 1929.

Saline extracts of macerated spleen pulp injected into tuberculous cattle caused an attenuation of the response to tuberculine, a quicker resorption of the tuberculous lesions and rapid calcification of the organs attacked. The animals treated showed no increased temperature or other indications that the material was toxic.—M. O. L.

**Internal secretions and immunity. II. The effects of ablation of the thyroids and the testes, and of the rate of agglutinin formation in active immunization by the typhoid bacillus (La sécrétion interne et l'immunité. II. De l'effet produit par l'ablation de la glande thyroïde, des testicules et de la rate sur la formation des agglutinines dans l'immunisation active par le Bacille de la fièvre typhoïde).** Botchkareff, P. V. and E. P. Tchernosatsky, *Russian J. Endokrinol.* 3: 100. 1929.

Ablation of the thyroids or of the testes caused a lessened capacity of formation of antibodies to the typhoid bacillus, and a decrease in the rate of formation of agglutinins.—M. O. L.

**Effect of thyroidectomy on the metabolic rate (both basal and maximum) (Influence de la thyroïdectomie sur le métabolisme énergétique [métabolisme de base et métabolisme de sommet]).** Chahovitch, X., *Compt. rend. Soc. de biol.* 100: 1220. 1929.

Removal of the thyroid in rats reduces the basal metabolism as is well known. It reduces also the maximum or summit metabolism as obtained by exposure to intense cold. Exposure to cold is known to be a powerful stimulus for adrenals and thyroid but the author in collaboration with Giaga pointed out that adrenalectomized rats completely lose their heat regulation when

exposed to cold. The conclusion was that the thyroid does not work in this circumstance if the adrenals are removed. The shivering process was not studied by the author though it plays an important role.

The influence of heredity in exophthalmic goitre. Cockayne, E. A., Arch. Dis. Childhood, 3: 227. 1928.

That the disease is so rarely present at birth, so variable in its date of onset and so often transmitted by apparently healthy parents, are facts which are more easily explained on the basis of an inherited constitutional weakness of the thyroid gland rather than of Graves' disease itself. The constitutional weakness is inherited as a dominant and some of those who inherit it may remain apparently healthy while others may develop any or all signs of the disease under the influence of injurious local geographical influences. The author reports four instances of exophthalmic goitre in one family.

—M. B. G.

Contribution to the study of "precocious matronism" (Contributo allo studio del matronismo precoce di Pende). De Candia, S., Riforma med. 45: 799. 1929. Abst., Rev. franç. d'endocrinol. 7: 336.

Pende has described, under the title of "precocious matronism" a new form of infantile obesity which until that time had been confused with cases of infantile adipose myxoedema, or with other adolescent body enlargements. It has to do with children of five to seven years of age at the most, who are rapidly growing fat. The change in shape is of the type usually met with in women of mature age, hence the name matronism. Pende considered this syndrome as resulting from a more or less serious hypothyroidism associated with a cortical hypersuprarenalism causing a precocious maturity of the genital glands. The author reports a case of this type in a young girl five years old. The child had the appearance of an adult. There was excessive body development, the proportions resembling the megalosplanchnic type. There was a relative decrease of calcium excretion with increased elimination of potassium and cholesterol with hyperuricemia and hyperglycemia. The basal metabolism was slightly lowered. The extra fat was very noticeable at the neck, in the region of the ribs, the breasts, the flanks, the belly and the buttock.

—Translated by J. Gagnon.

Further studies of the thyroid gland. V. The thyroid gland as a growth-promoting and form-determining factor in the development of the animal body. Dye, J. A. and G. H. Maughan, Am. J. Anat. 44: 331. 1929.

Young dogs were used in these experiments, complete litters being employed. Half of the puppies, usually the larger ones, were thyroidectomized when five to six weeks of age; the remaining half were kept as littermate controls. The selection was always made so that the experimental and control animals were of the same sex. A comparison was first made between the thyroidless cretin and its control littermate, as used in a single experiment, then a composite comparative analysis of all animals was made. Careful measurements were taken to record body growth in control and experimental animals. After autopsy the skeletons were prepared and various measurements taken. As a result of their studies the authors conclude that the thyroid gland normally exerts a very marked stimulating influence on the growth impulse of the various parts of the animal body. They find that the retardation of growth following extirpation of the thyroid in young pups does not affect all parts of the body equally. The retardation of the body as a whole is greater than of the skeletal system, and the individual bones are not affected to the same extent in all proportions. In general, the modifications are similar in all bones, viz., an absolute retardation of growth in length, weight and volume and in the epiphyses. Bone growth from endochondral and epiphyseal plate ossification is strikingly retarded, while sub-periosteal and membrane bone formation are little or not at all retarded and may even be accelerated. The oxygen-consuming power of surviving skeletal muscle is reduced to 68.1 per cent of its normal level. Bone growth is affected in the same direction, but with the exception of growth in weight, which is reduced to 68.9 per cent of the normal values, is affected less than that of the "fundamental" tissue metabolism. This is probably due to the lower level of bone metabolism as compared with muscle, viscera, etc.—W. J. A.

Pregnancy complicating simple goitre and Graves' disease. Gardiner-Hill, H., *Lancet*, 216: 120. 1929.

An analytical study of histories of twenty-six cases of simple goitre and eighty-nine cases of Graves' disease to determine the incidence and effects of pregnancy. The incidence of pregnancy was average in cases of persistent adolescent goitre but below average in simple goitre in adult life, especially if symptoms of hypothyroidism were present. Pregnancy was followed by increased hypertrophy of thyroid gland and hypothyroidism. Miscarriages were more frequent in the presence of hypothyroidism. When Graves' disease was present the incidence of pregnancy was low, and premature births and miscarriages were more frequent. Conception usually occurred during a remission of the disease. During pregnancy there was usually amelioration of the symptoms of Graves' disease. Persistent improvement after pregnancy terminated was noted more frequently in cases which went to full term. Frequent miscarriage or premature birth may be attributed to shock, mental stress, inadequate rest, for where satisfactory conditions were attained and mental stress was minimized the results were generally good. The number of simple goitres reviewed is too small to justify conclusions. The author states that his findings in Graves' disease differ from the reports of Plummer and others. Dissimilarity of symptoms of goitre according to the locality may account for the variations reported.—J. P. Pratt.

Insulin in the treatment of hyperthyroidism (*Insuline dans le traitement de l'hyperthyroïdie*). Goffin and J. Slosse, *Presse méd.* 37: 440. 1929.

The authors administered insulin in doses as high as 60 units to patients with hyperthyroidism in whom the customary treatment had been ineffectual. The results were followed up for a period of two years. In the majority of these cases there occurred a retardation of the pulse rate, increase in weight, and a lowering of the basal metabolism.—I. B.

Masked hyperthyroidism. Hamburger W. W., *Tr. A. Am. Physicians*, 44: 348. 1929.

A series of cases of atypical thyrotoxicosis are presented illustrating the difficulties of diagnosis and the frequency with which disturbances of the thyroid gland masquerade as other disease entities. The cases presented include: a case of persistent grave hyperemesis and dysphagia necessitating nasal feeding; a case of cardiorenal-vascular disease with arterial hypertension and heart failure; a case of supposed severe diabetes mellitus with secondary hypoglycemia following massive insulin injections; a case of long-standing chronic myocarditis of unknown etiology; a case of rheumatic mitral stenosis and insufficiency and aortic insufficiency with paroxysmal auricular tachycardia and unrecognized thyrotoxicosis; a case of angina pectoris with unrecognized substernal goiter, and others. The crucial diagnostic findings are considered to be the presence of a persistently elevated metabolic rate unexplained by other conditions, and the relief of symptoms following iodine medication or thyroidectomy.—I. B.

Structure of the thyroid gland in toxic goiter. Harsha, W. T., *M. Clin. North America*, 23: 501. 1929.

This contribution is particularly valuable for its photomicrographs. One feature not usually accentuated in the consideration of thyroid pathology is the lymphatic hyperplasia found in the thyroid in some toxic cases. Central areas of lymphatic hyperplasia are made up of lymphoblasts with many active mitotic figures. The lymphocyte count in some of the more toxic cases is occasionally high—50 to 70 per cent small lymphocytes. In two cases massage of the thyroid gland for 10 minutes resulted in an increase of lymphocytes in the circulating blood. In one case the increase was from 40 per cent prior to massage to 78 per cent 6 hours later. In the other case in which massage was attempted, the increase was from 57 to 62 per cent. No control by massage elsewhere was made. In one case of toxic goiter the basal metabolism was increased from plus 46 per cent prior to massage to plus 80 per cent following a 15-minute manipulation of the thyroid gland after 6 hours, and it required 36 hours for the B.M.R. to reach plus 50 again. In two other cases there was no increase in the basal metabolism following massage.—I. B.

An etiological study of primary Graves' disease with special reference to the significance of the sex events of the female. Hill, H. G., *Quart. J. Med.* 22: 217. 1929.

This paper is a valuable contribution serving to emphasize the causal relationship of psychic trauma and sex epochs in Graves' disease. Two hundred and six cases of primary Graves' disease were studied. Of these cases, 183 were females and 23 males, a ratio of 8:1. Of the 183 females, 32 were adolescent, 63 single, and 88 married women. Of the males, 6 were adolescent, 4 single, and 13 married men. The incidence of the disease was almost entirely limited to the period of active sex life, only one case occurring before puberty and only 5 after the climacteric. In 80% of these cases the disease was precipitated by extrinsic factors, shock, mental stress, and sepsis. In 50% the 2 former factors, in 20% the latter, whilst in 10% they were combined. In the remaining 20% there was no apparent extrinsic exciting factor. The sex events in the female—puberty, pregnancy, the puerperium, and the climacteric—appear to be important predisposing factors, for the incidence of cases was considerably greater at these times. 56.6% of the adolescent and 76.2% of the climacteric cases developed the disease within 3 years of these events. Of the 71 cases in married women during the child-bearing period, 41 developed the disease during pregnancy, the puerperium, or after miscarriage. The incidence during the puerperium was double that during pregnancy. Of the 71 cases in married women during the child-bearing period, 14, or 19.7%, had had no pregnancy prior to the onset of the disease; 13, or 18.3%, had had only 1 pregnancy; and 15, or 21.1%, developed the disease during their first pregnancy or puerperium. Of the 21 climacteric cases, 17 were married and 4 single. Seventy-two per cent of the former had had 2 or more pregnancies. The low incidence of cases at the climacteric in single women is in keeping with the general decrease in incidence in single women in later life.—I. B.

The ovary in experimental hypo- and hyper-thyroidism. II. The influence of experimental hyperthyroidism on gestation. Kunde, M. M., A. J. Carlson and T. Proud, *Am. J. Physiol.* 88: 747. 1929.

Cretin rabbits were produced by the removal of the thyroid at the age of three weeks and the animals were allowed to remain in the cretin stage for several months. They were then fed desiccated thyroid until symptoms of hyperthyroidism resulted, and then sacrificed. Histological section of the ovaries revealed a large number of primary follicles and apparently normal Graafian follicles in all stages of development. In rabbits with severe hyperthyroidism thus experimentally produced, the processes of oestrus, ovulation, fertilization, migration and implantation take place, but in most instances the young are never born, resorption occurring instead. Resorption of all or many of the fetuses occurs during the latter two-thirds of the pregnancy.

—M. B. G.

Further observations on latent hyperthyroidism masked as heart disease: angina pectoris. Levine, S. A. and G. L. Walker, *New England J. M.* 202: 1021. 1929.

A general discussion is followed by eleven brief case histories. The presenting symptoms are those of cardiac disease. Exophthalmos and enlargement of the thyroid are absent, but tremor, sweating, a feeling of warmth, together with loss of weight and attacks of diarrhea, are suggestive. The skin tends to be warm, moist, and pigmented, and to have a peculiar salmon color. The patient is more nervous and alert than one would expect him to be with such a degree of illness. These conditions suggest the diagnosis of hyperthyroidism, which must, however, be confirmed by a study of the basal metabolism. In such cases proper surgical intervention yields very satisfactory results.

—J. C. D.

Specimens from a case of malignant goiter. Moncrieff, A., *Proc. Roy. Soc. Med.* 23: 1. 1929. (Sect. Dis. Child.).

The patient was a girl aged 11 years. There was no family history of goiter. Swelling of the neck was first noticed at the age of 4. She had lived in Scotland most of her life except for a trip to Australia. For the few months previous to her admission to the hospital there had been increasing noisiness in respiration and the thyroid had become larger. Adenomatous goiter was

diagnosed but thyroidectomy proved to be very difficult owing to adhesions, especially of the deeper portions of the gland. The child succumbed 12 hours after the operation. Only a limited examination of the operation area was permitted, but it was then found that the deeper portions of the gland were very hard and were adherent to the deeper structures of the neck. In one place the trachea was infiltrated with growth which protruded through, just below the larynx. Microscopical examination of the superficial portions of the gland showed a parenchymatous type of goiter, while in the deeper portions malignant changes were observed.—I. B.

**Hyperthyroidism associated with abdominal lesion.** Priest, W. S., M. Clin. North America, 13: 483. 1929.

This contribution is essentially a discourse on two illustrative cases of so-called hyperthyroidism associated with abdominal lesions, and a discussion on causal relationship. In one of these cases the abdominal condition was in the nature of a low-grade infection; in the other there was a primary carcinoma of the head with possible abdominal metastases.—I. B.

**Roentgentherapy of Graves' disease and its dangers (Die Roentgentherapie der Basedowkrankheit und Ihre Gefahren).** Rahm, H., Klin. Wchnschr. 24: 1131. 1929. Abst., Arch. Physical Therapy, 11: 44.

It is out of the question to consider roentgenotherapy in exophthalmic goiter as not dangerous. A great many deaths have been described, partly due to the hyperthyreotic response following irradiation, partly to lesions of the larynx. Another danger is given by the possibility of Graves' disease being converted into myxoedema. A further source of danger is the fact that roentgenotherapy may hamper the timely chance that operation would afford. Pre-operative roentgenotherapy is not without dangers, unless basal metabolism be controlled.

**Effects of combined administration of extracts of anterior lobe of pituitary and of potassium iodide on thyroid gland.** Silderberg, M., Proc. Soc. Exper. Biol. & Med. 27: 166. 1929.

Fourteen guinea pigs were fed KI daily in doses of .05 or 0.1 grams. From the tenth to the seventeenth days, 10 of the pigs were given daily intraperitoneal injections of 1cc. of an acid extract of anterior pituitary substance. Both the KI and the pituitary extract exerted their specific effects on the thyroid gland, not in summation but in separate areas, giving a mosaic of areas in which one or the other effect predominated. The typical effect of the anterior lobe extracts was to cause hypertrophic acinus cells, absorption of the greater part of the colloid and irregular acini. The KI effects were a considerable increase in mitoses, a slight increase in the size of the cells and a slight softening of the colloid.—M. O. L.

**Modifications of the precipitation of erythrocytes with respect to the condition of the thyroid (Modifications de la reaction de precipitation des erythrocytes en rapport avec le fonctionnement de la thyroïde).** Tchernosatsky, E. P., Russian J. Endokrinol. 3: 126. 1929.

The sedimentation velocity of the erythrocytes was studied in 146 sheep and 14 rabbits before and after thyroidectomy and after the administration of thyroid substance, and in 27 patients with thyroid disorders. In the sheep, the sedimentation rate was between 3 and 11 mm. per hour and in the rabbit 3 to 6 mm. per hour. After thyroidectomy, the sedimentation rate decreased, being slowest 4-6 weeks after the operation. In the sheep, the administration of dried thyroid substance in doses of 0.02-0.06 grams per kgm. caused a marked increase in the sedimentation velocity. The administration of iodine in the form of Lugol's solution also caused an accelerated sedimentation rate, but less marked than thyroid substance. The sedimentation rate appears to be increased in patients with hyperthyroidism and decreased in patients with hypothyroidism, and the author believes that this is of diagnostic value.

—M. O. L.



The influence of the thyroid gland on the circulatory blood volume and the blood depot of the organism (*Der Einfluss Der Schilddrüse Auf Die Zirkulierende Blutmenge und Die Blutdepots Des Organismus*). Preliminary Report. Wislicki, L., *Klin. Wchnschr.* 8: 1568. 1929.

Wislicki says that in Basedow's disease, through the increase of basal metabolism, there is a definite increase of the minute volume of the blood. In contrast the opposite is found in myxedema and obesity. Noting this difference in the blood volume in hyperthyroidism and myxedema, Wislicki studied the blood volume of hyperthyroid cases. He used the Trypan red method of Seyderhelm and Lampe and the blood estimation was taken after rest in bed and at least three and one-half hours after breakfast. In healthy individuals the plasma volume was 38-45 cc. per kgm. The question arose whether the increase of the blood volume in Basedow's disease was a non-specific reaction of the organism in response to the increased circulation or if it was a specific reaction of the thyroid gland. He therefore gave thyroid medication to see its influence on the circulating blood volume. In cases of obesity it was shown that the blood volume increased by the giving of thyroid extract, the patient lost weight but at the same time the metabolism increased. In cases in which the medication produced palpitation of the heart without achieving the increase in basal metabolism, it was noted that there was no influence on the blood volume. In myxedema after thyroid medication, the blood volume increased one to one and one-half times. Wislicki experimented on thyroidless animals in which the carbon dioxide was artificially increased in the circulation. He was unable to demonstrate any carbon dioxide in the spleen. The blood channels of the spleen apparently remained closed after thyroidectomy. The longer the time between the thyroid extirpation and the experiments, the greater the amount of carbon dioxide could be introduced in the blood without producing carbon dioxide in the spleen. The addition of thyreiodin or thyroxin opened up the channels in the spleen so that a normal reaction was obtained. Therefore, we can say that the thyroid has a function which influences the blood depot.—R. C. Moehlig.

The incidence of goiter among adults in Nashville, Tennessee. Youmans, J. B., *South. M. J.* 22: 966. 1929.

Eighty-five goiters were found among 500 adult colored and white patients of both sexes, a total incidence of 17%. A much higher incidence was found in women at certain age periods, the maximum (42%) occurring in white women during the fifth decade. The total incidence was about four times greater in women than in men, and was slightly less among colored than among white patients. Both white and colored women showed an increasing incidence with advancing age up to a maximum at the fifth and sixth decades, respectively. Men showed a maximum incidence during the second and third decades with a sharp drop thereafter, and a secondary rise in the colored men at 40 to 49. The occurrence of goiter in this locality may probably be attributed in part to primary iodine deficiency, although sufficient data in regard to the iodine supply of the region is not available to determine this definitely. It is suggested that improper diet and poor hygienic conditions may be additional factors of etiologic importance in the group studied.—Author's Summary.

# ENDOCRINOLOGY

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## ENDOCRINE DYSFUNCTIONS IN RETARDED CHILDREN AND THEIR RESPONSE TO TREATMENT\*

CARLETON J. MARINUS, M.D.

DETROIT

and

O. P. KIMBALL, M.D.

CLEVELAND

Ten years ago the late Dr. Theodore McGraw, Jr., who was well known to many of the members of this organization, began a study of the endocrine conditions to be found among the children in the special classes of the Detroit schools. He found that twenty per cent of these children showed obvious signs of endocrine disturbance.

### METHOD OF STUDY

In the Detroit School System all children who are unable to keep up with regular school work, or those with an intelligence quotient of less than 80 per cent and more than 47 per cent, or a mental age of 5 years, are placed in special classes. All below this level are removed from the regular schools and placed in an institution for the feeble-minded. Our study is limited to the children in the Special Classes.

We started with the conception that any endocrine disturbance of sufficient severity to produce mental retardation must inevitably produce detectable physical signs, such as retarded physical development, by which it should be possible to diagnose the type of glandular disturbance. With this idea in mind, we therefore went to the Special Schools and made an inspection of the children. We observed particularly:

The height and weight in proportion to the age.

The body proportions.

Facies.

Skin, hair and nails.

Stigmata of deviation.

Physical defects such as teeth, tonsils or anemia.

Development of genitalia in the boys.

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As a result of this preliminary inspection the children were grouped into three classes: (1) those showing correctable physical defects (chronic infection, anemia, visual defects, malnutrition, etc); (2) those showing definite signs of disturbed development suggestive of endocrine dysfunction; (3) those showing no physical or endocrine abnormalities. The members of the first group were turned over for treatment to the regular Medical Department of the Board of Health. The members of the second group were brought to the Clinic for further study.

In each case one or both of the parents accompanied the child to supply an opportunity for estimating the factor of heredity and to give the birth and infancy history. In each case a trained social worker (Mrs. Reba Talbott Aldrich) visited the home to study the environmental situation and to estimate its influence upon the problem. This contact was extremely valuable in securing the cooperation of the family. In the Clinic the child was thoroughly examined, physical measurements were made, and indicated laboratory studies such as basal metabolism, blood count, Wasserman and x-ray examinations were made.

#### DIAGNOSIS

The pineal, thymus, sex glands, and suprarenal cortex are probably of greater or less importance in the physical development of the growing child. The pineal, in particular, has been thought to affect mental development. No exact methods of diagnosis of disturbance in the function of these glands have been developed, and attempts at therapeutics have not been successful.

We were left then with the thyroid and pituitary glands as possible causes of defective mental development. In both cases we have available potent extracts capable of producing definite physical effects. In both cases definite physical signs of the glandular deficiency are recognized, making possible the diagnosis of a deficiency.

Our cases of thyroid deficiency have fallen into three groups. (1) In *Clinical Hypothyroidism*, the physical signs of deficiency were present at the time of examination. The subjects showed the cretinoid type of facies, the hypothyroid type of obesity, short, stubby fingers, undergrowth, subnormal temperature, dry skin, tendency to anemia, and low basal metabolism. This type has been adequately described in the literature. (2) In *Congenital Hypothyroidism*, the children at the time of examination may show none of the signs of hypothyroidism as usually recognized. The diagnosis is made on the basis of the family history, presence of goitre in the mother during pregnancy, excessive weight at birth, delay in teething, walking and talking, infantile malnutrition or obesity, and a characteristic failure of physical development which gives a slender, poorly developed skeletal system, tendency to carious teeth, relative overgrowth of the long bones (approaching the eunuchoid type of body build), unstable nervous system and malnutrition. This type gives a normal or high metabolic

rate upon their first test, but the true basal rate is low when obtained upon repeated tests. Their tolerance to thyroid extract is higher than normal. This type corresponds to the "forme fruste" type described in the literature. (3) Instances of *Congenital Goitre* were also noted. The subjects usually give a family history of goitre and show upon examination a thyroid gland which contains palpable nodules or a persistent pyramidal lobe, or both. The gland might be larger or smaller than normal, and soft or hard, depending upon the age of the child (whether in puberty or not) and the amount of iodine that the child had received. This group might also show the characteristics of group one or of group two, or might present a perfectly normal physique except for the abnormal gland.

The pituitary dysfunctions were classified as: (1) *Bilobar Pituitary Deficiency* (Froehlich's Syndrome) and (2) *Anterior Lobe Deficiency*. The characteristic distribution of obesity, genital aplasia and lack of physical energy characteristic of bilobar deficiency have been well described in the literature. Anterior lobe deficiency without posterior lobe involvement is difficult of differentiation from the "forme fruste" type of hypothyroidism. It is characterized by a lack of skeletal and muscular development with retention of the infantile body proportions and genital hypoplasia. The family history gives no evidence of thyroid disturbance and the history of the infancy does not reveal the characteristic physical retardation. The diagnosis was made by exclusion, and it seemed probable to us that many cases in our "Anterior Lobe Deficiency" group were primarily subjects of hypothyroidism, with secondary pituitary failure.

Many cases were found showing evidences of failure of both the thyroid and the pituitary. Cases of achondroplasia, microcephalia, mongolism, erythroelidism, etc., which may be of endocrine origin, were found and are included under a miscellaneous group.

We were struck by the number of children in whom the parturition history gave evidence of mild birth injury. These children frequently came from parents of good intelligence and good endocrine make-up. In these children the signs of endocrine disturbance were frequently present, but it was felt that the brain injury was probably the more important factor.

#### TREATMENT

The subjects of thyroid insufficiency were given desiccated thyroid substance in increasing doses until definite evidence of overdosage was obtained. The dose was then reduced to the largest amount the child could tolerate, leaving slight evidence of overdosage such as mild tachycardia on exertion, etc. It was felt that a slight excess was necessary to insure that the full dosage was given and it was believed that this would do no harm if the child were under observation. The dosage was checked at intervals by repeated basal metabolism tests, and in no case was the rate maintained at a level more than five per cent above normal. The subjects of

pituitary insufficiency were given 15 grains of desiccated anterior lobe substance, of a preparation known to have definite potency in that dosage. This quantity was obviously too small in the more severe cases, but because of the expense of the material we could not further increase the dosage.

The children returned to the Clinic each month, where observations were made of their height, weight, pulse rate, general condition, etc. At this time the observations of the parents as to their behavior and physical condition were noted. We received from the teacher in direct charge of the patient a bi-monthly report in which she gave her observations regarding behavior, application, attention span, self-control and interest. The teachers understood that these pupils were being studied in the Clinic but did not know which were receiving treatment and which were being carried as controls. This precaution was taken to eliminate the factor of personal bias. At suitable intervals complete psychological tests were performed which could be compared with one or more of the routine tests performed before the study was undertaken.

MATERIAL AND EXPERIMENTAL DATA

In all, 3585 children were examined; of these 667, or 18.6 per cent showed definite evidence of endocrine disturbance. Of this group, approximately two-thirds were subjects of thyroid deficiency—the other third pituitary deficiency. We found 65 cases of birth injury with developmental disturbances suggesting endocrine dysfunction. There were 85 cases of congenital syphilis. The following tabular analysis indicates some of the more interesting results of the study:

Inspections in schools.....	3585
Correctable physical defects.....	1159
Possible endocrine cases.....	993
No endocrine defect.....	1433
Cases studied in Clinic.....	903
Eliminated as non-endocrine.....	236
Endocrine cases .....	667
Per cent of total examined.....	18.6
Number under active treatment.....	233
Number under control study.....	151
Basal metabolism tests.....	450
Other laboratory examinations.....	200

Four series of data were collected:

1. Progress in school as reported by the individual teachers.
2. Intelligence Quotients (Binet tests).
3. Achievement records (performance on the Pressey and the Stanford scales).
4. Motor and co-ordination tests (performed by L. E. Krumholz).

## SCHOOL PROGRESS

*Hypothyroidism*

Treated.....	21
Improved .....	17 or 80%
Markedly improved .....	9 or 43%
Unimproved .....	4 or 20%
Controls .....	11
Improved .....	5 or 46%
Unimproved .....	4 or 36%
Definite decline in mark.....	2 or 18%

*Congenital Hypothyroidism (with and without Goitre)*

Treated .....	132
Improved .....	101 or 76%
Unimproved .....	31 or 24%
Controls .....	56
Improved .....	24 or 43%
Unimproved .....	32 or 57%

*Pituitary Deficiencies*

Treated .....	39
Improved .....	35 or 90%
Markedly improved .....	9 or 23%
Unimproved .....	4 or 10%
Controls .....	30
Improved .....	17 or 57%
Unimproved .....	13 or 43%

*Combined Thyroid and Pituitary Deficiency*

Treated .....	21
Improved .....	15 or 71%
Unimproved .....	6 or 29%
Controls .....	13
Improved .....	6 or 46%
Unimproved .....	7 or 54%

*Miscellaneous*

Treated .....	20
Improved .....	15 or 75%
Unimproved .....	5 or 25%
Controls .....	6
Improved .....	2 or 33%
Unimproved .....	3 or 50%
Declined .....	1 or 17%

An analysis of the school progress in the thyroid deficiency groups shows that in more than one-half of the cases without treatment the tendency is to failure of improvement, or even poorer school work. This tendency is more marked in those cases in which the thyroid deficiency is evident at the time of examination. This finding is corroborated by the intelligence tests. The mentally deficient child with hypothyroidism shows a definite tendency to a falling intelligence quotient, this tendency being most marked if signs of hypothyroidism are still present. Forty-seven per cent of those showing congenital hypothyroidism, and 55 per cent of the actively deficient cases show a falling intelligence quotient. Ten to twenty per cent of both groups, however, show a slowly rising intelligence quotient. No explanation has been found for this fact.

## INTELLIGENCE TESTS

*Hypothyroidism*

Treated—	
Rising I.Q. ....	14%
Falling I.Q. ....	38%
Same I.Q. ....	48%
Controls—	
Rising I.Q. ....	27%
Falling I.Q. ....	55%
Same I.Q. ....	18%

*Congenital Hypothyroidism (with and without Goitre)*

Treated—	
Rising I.Q. ....	14%
Falling I.Q. ....	24%
Same I.Q. ....	62%
Controls—	
Rising I.Q. ....	0%
Falling I.Q. ....	75%
Same I.Q. ....	25%

*Pituitary Deficiencies*

Treated—	
Rising I.Q. ....	14%
Falling I.Q. ....	22%
Same I.Q. ....	64%
Controls—	
Rising I.Q. ....	10%
Falling I.Q. ....	27%
Same I.Q. ....	63%

*Combined Thyroid and Pituitary Deficiency*

Treated—	
Rising I.Q. ....	0%
Falling I.Q. ....	47%
Same I.Q. ....	53%
Controls—	
Rising I.Q. ....	10%
Falling I.Q. ....	43%
Same I.Q. ....	47%

*Miscellaneous*

Treated—	
Rising I.Q. ....	10%
Falling I.Q. ....	30%
Same I.Q. ....	60%
Controls—	
Rising I.Q. ....	0%
Falling I.Q. ....	20%
Same I.Q. ....	80%

The improvement in school work resulting from treatment is confirmed by the results of the Binet tests. In no single case was a marked increase in intelligence noted, but there is a significant tendency to prevent the expected fall in intelligence. Whereas before treatment 55 per cent of the children showed a falling intelligence quotient, but 38 per cent showed a fall during the treatment. Conversely, whereas 45 per cent remained stationary or rose slowly before treatment, 62 per cent held their own or better during treatment. This is particularly significant in view of the fact that many of the children were not treated continuously during the entire period between their tests.

The cases of pituitary insufficiency do not show as marked a tendency to falling intelligence quotients as was noted in the thyroid groups, only 27 per cent registering a fall. No change is noted in the percentages obtained after treatment.

## ACHIEVEMENT TESTS

*Hypothyroidism*

Treated—	
Improved .....	70%
Unimproved .....	30%
Controls—	
Improved .....	80%
Unimproved .....	20%

*Congenital Hypothyroidism (with and without Goitre)*

Treated—	
Improved .....	81%
Unimproved .....	19%
Controls—	
Improved .....	55%
Unimproved .....	45%

*Pituitary Deficiencies*

Treated—	
Improved .....	70%
Unimproved .....	30%
Controls—	
Improved .....	80%
Unimproved .....	20%

*Miscellaneous*

Figures not adequate for analysis.

The progress in achievement, as determined by the Stanford tests in the older and by the Pressey tests in the younger children, gives the same results. In the untreated congenital hypothyroid group 55 per cent showed an average gain of 7 months, 33 per cent a loss of 5 months, and 12 per cent no change. During treatment 81 per cent gained an average of 8 months each, and 19 per cent lost or remained the same.

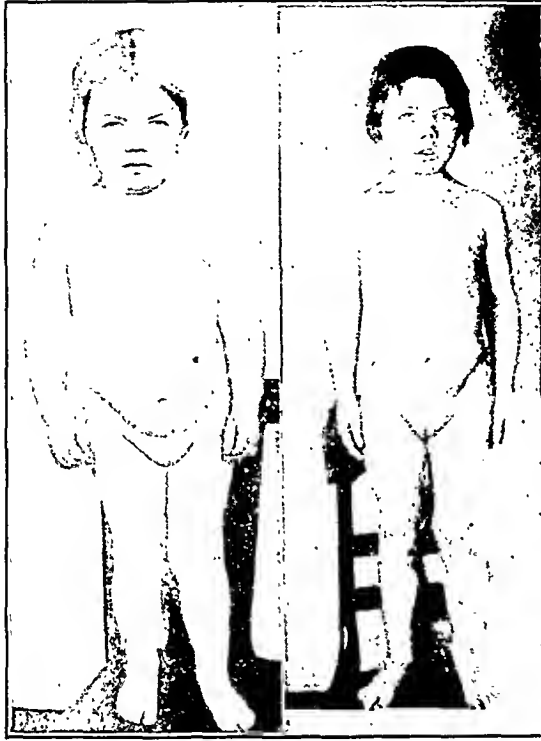
The achievement figures were identically the same in the pituitary group, whether treated or untreated, namely, 70 per cent gain and 30 per cent loss. Here again it will be noted that the pituitary group does not show the tendency to retrogression nor the benefit of treatment recorded in the thyroid groups.

The studies of Mr. Krumholz on the motor functions (speed, steadiness, muscular co-ordination) fail to show any significant trend in any group, whether control or under treatment. This line of investigation is entirely new, and may yield significant information after further study.

A single case history will serve to illustrate in a concrete way the facts presented above. V. M., a girl of 11½, was diagnosed as suffering from hypothyroidism. The family history was devoid of data of endocrine



significance. The birth weight was 8 pounds. In babyhood the patient was lethargetic and extremely constipated. Her first teeth appeared at 13 months; walking and talking began at 13 months. The basal metabolic rate before treatment was  $-13$  per cent; while taking thyroid substance in dosage of  $1\frac{1}{2}$  grains the rate was normal.



(A)

FIG. 1.

(B)

(A)—V. M., age 11 years, 2 months—Before treatment.  
 (B)—V. M., age 12 years, 2 months—After thyroid treatment. Loss of weight, 2 lbs. Gain in height,  $4\frac{1}{2}$  in.—(Courtesy Harper Hospital.)

Her school progress showed well marked improvement. She gained 4 months by the Pressey scale. Her intelligence quotient increased from 55 per cent to 58 per cent. The change in her physical condition can be visualized from accompanying illustration. It will be noted that the physical change from treatment was significantly greater than the mental development.

#### DISCUSSION

It is our impression that faulty thyroid function in a pregnant woman interferes with the normal development of the central nervous system to a degree depending upon the severity of the thyroid deficiency at different stages in the development of the fetus. This is associated with a disturbance in the development of the fetal thyroid gland, which is demonstrated as a congenital goitre or the picture of congenital hypothyroidism. This thyroid disturbance may undergo spontaneous improvement during the life of the child, with a disappearance of the signs of active hypothyroidism.

Supplying the deficiency of the thyroid hormone enables the poorly developed central nervous system to function at a better rate and more efficiently. It does not, however, repair the damage that has already been done.

Obviously, the earlier the defective secretion is replaced, the less damage will be done, and the more complete will be the clinical improvement. The real solution of the problem lies in the correction of the faulty thyroid function of the pregnant mother.

The children who have already come into the world with this handicap should be given the benefit of adequate thyroid replacement therapy as early as possible, and this treatment should be continued as long as the need for it exists.

It is our hope that this study will stimulate the school authorities and physicians in touch with these problems to the early recognition and proper treatment of these cases.

Our results in pituitary deficiency do not indicate a significant relationship between this condition and mental retardation.

Pituitary treatment, in the dosage supplied, did not significantly alter the intelligence, although there was an improvement in school work, probably due to the stabilizing effect of treatment upon the personality.

#### SUMMARY AND CONCLUSIONS

Thirty-five hundred children have been studied, with the isolation of 667, or 18.6 per cent, who showed definite signs of endocrine deficiency. Nearly 400 of these children have been followed either as controls or while taking the indicated treatment.

The reports of the individual school teachers, the results of intelligence tests, and of the specific achievement tests give parallel findings. In the thyroid deficiency groups there were noted:

1. A tendency to falling intelligence quotient, decreased aptitude in school and achievement by the special tests.
2. A tendency to the prevention of this fall under treatment.
3. Greater physical than mental improvement under treatment.

In the pituitary deficiency groups there were noted:

1. Less marked tendency to falling intelligence quotient and achievement without treatment.
2. No change in intelligence or achievement as a result of treatment.
3. Improvement in school work unaccompanied by evidence of increased mental development.

These results are entirely in accordance with those reported by Dr. Fox.

We wish to express our gratitude to the entire personnel of the Department of Special Education for their loyal and efficient co-operation in this study; to Parke, Davis & Company, who donated all the Pituitary Extract used in the first year of the study; to Dr. Harry Clark, who performed without recompense over 200 laboratory examinations, and to the Research Committee of the Detroit Board of Education, whose interest and assistance made this work possible.

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## PITUITARY HEADACHE\*

LAURENCE H. MAYERS, A.M., M.C.  
Medical Service "A," St. Luke's Hospital  
CHICAGO

This discussion presents five comprehensive case histories in which the clinical picture and treatment course are typical of a series of 60 cases considered under the general category of pituitary headache. The sixty cases are the result of careful selection from patients referred by the gynecological department of St. Luke's Hospital, Chicago, between the years 1921 and 1925 from a clinic which clears about nine hundred patients annually. Our experience would seem to indicate that about 16 out of 1,000 cases of the headaches that constitute so great a problem in the clinical handling of gynecological patients are proper subjects for pituitary therapy.

The usual subjects of pituitary headache are obese women of long-legged, short-waisted build. They are energetic, alert and intelligent. All are subject to such menstrual dyscrasias as amenorrhea, dysmenorrhea, or menorrhagia. The same patient may exhibit all of these conditions at different points in her history, and all show the common history of onset at adolescence, during the first years of married life, or subsequent to childbirth. There is often a family incidence. From patient to patient and in the same patient at different times there is a wide range of variation in symptom complex and treatment response, and the relative constancy of general outline carries no corollary of uniform treatment or fixed response. Each case presents an individual and engrossing therapeutic problem. It is for this reason that the treatment course of our cases is reported with considerable detail and over a much longer period than has been the rule in current literature on the subject.

### CASE REPORTS

*CASE I:* E. A., female, colored, unmarried, age 20 years, was examined November 12, 1923. She had habitual headache which became progressively worse and was intensified when menses began at the age of 12. These headaches occurred daily since 1921, were exaggerated during menses, confining her to bed. The attacks were four to twelve hours in length, coming on during the day, never at night and never interfering with sleep and usually continued until the patient went to sleep. The headaches, located deep over the left eye were worse on stooping and gradually became generalized and bursting in type, causing a dazed sensation. Excitement induced and intensified the symptoms. There was no sense of anything moving in the head. Nausea, occurring at the climax, brought relief. Aspirin in ten grain dosage was helpful. The headaches were followed by sluggishness and an overpowering sense of fatigue, drowsiness and melancholy. The patient was tired all of the time and neither work nor play could interest her. She was irritable, noises annoyed her and solitude was desired. She was unusually advanced in her school studies, but backward in all

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social situations. She avoided men and seemed to understand nothing about sexual desire. Glasses had afforded but slight temporary relief and many other forms of treatment had been quite fruitless.

*Physical Examination:* The patient appeared serious and unhappy. She was tall and fairly well built, but her legs were disproportionately long and her waist was short. Her figure was rather masculine. The hair on the head was abundant and coarse; some was evident on the upper lip. Pubic hair was masculine in distribution, and extended to the umbilicus. No abnormal hair growth appeared on the arms or legs. The legs were straight and masculine;

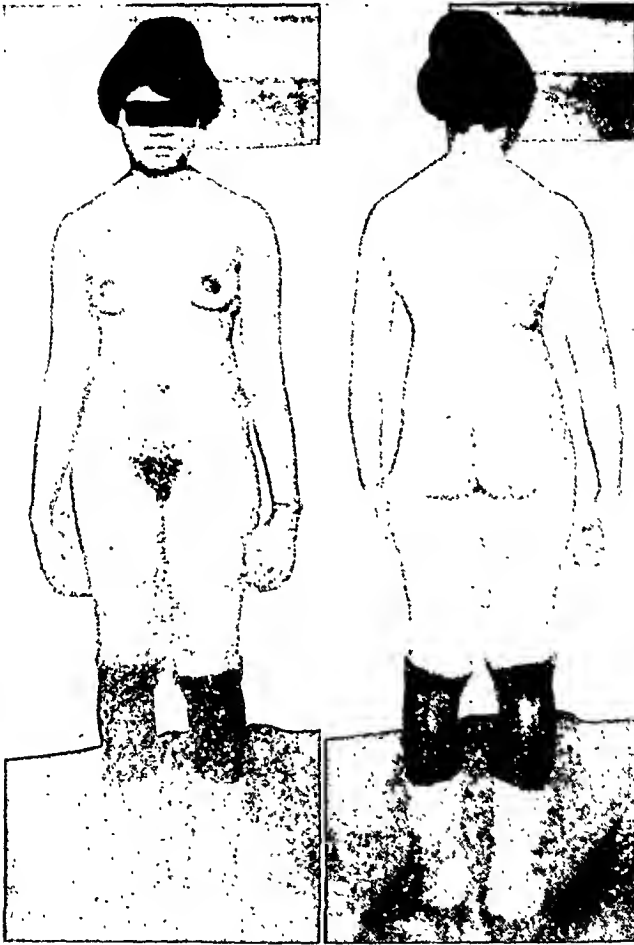


Fig. 1

Fig. 2

Fig. 1. Case 1, E. A., showing masculine distribution of pubic hair.

Fig. 2. Case 1, E. A., illustrating short waist and long legs typical of altered bone metabolism due to pituitary dysfunction.

the gait and posture were normal. The head was normal in size and the eyes were normally spaced. Refraction had been corrected by glasses. Pressure over supra-orbital region elicited tenderness. Visual fields were not taken. The features were coarse and the superior maxilla prominent. The upper central incisors were separated. The thyroid was not enlarged and was free from pulsation.

Roentgenogram of the sella showed no evidence of tumor. The space between the anterior and posterior clinoid processes measured about 5 mm.

The chest was well developed. The heart and lungs were normal. The pulse rate was 102, blood pressure 116-68. Blood sugar test was not made. The abdomen and abdominal organs were normal. The external genitalia were infantile. The uterus was small; tubes and ovaries were not palpable.

*Treatment:* Three subcutaneous injections of Burroughs & Wellcome's infundin (pituitary infundibular extract) in 0.5 cc. doses daily caused the patient to declare she "felt like a different person." She remained free from headaches, while receiving treatment as outlined, but the headaches, never so severe as prior to the administration of pituitary extract, tended to return when medication was interrupted. Whole gland treatment by mouth was substituted when the patient left Chicago.

Medication was interrupted, however, and in February, 1924, the headaches, becoming more severe, compelled her to return to the city. Infundin then administered three times a week and supplemented with whole gland pituitary extract by mouth again controlled the symptoms.

Observations made at four week intervals until June, 1926, showed the patient to be still free from symptoms (Figs. 1 and 2). The patient was last seen a year ago and is entirely free from symptoms.

*CASE II:* M. R., female, white age 21, was examined at the gynecological clinic in March, 1922, on the suggestion of oculist to find constitutional cause of dysmenorrhea and headaches, which persisted in spite of corrected refraction. Menstruation began at 16 with menorrhagia for five or six months, alternating with amenorrhea for five or six months. Development had been normal during growth period, but weight had increased from 115 to 145 pounds since 1920. Her



Fig. 3. Case II, M. R. The upper teeth exhibit the marked separation frequently found in pituitary types.

appetite was normal and she had never been constipated. Five brothers, four sisters, father and mother were living and well. There was no family history of similar complaints.

The patient had some headache all the time since her early teens. It started in the morning and continued throughout the day without remission. The pain was usually over both eyes, never bursting in type, nor resulting in a dazed sensation. There was not tenderness on deep pressure nor sense of anything moving in the head. The headaches were worse during menstruation, confining the patient to bed. Excitement brought on or intensified the pain and stooping made it worse, as did the consumption of sweets. No nausea nor vomiting occurred at the climax. Coal tar analgesics gave no relief. Her activities were reduced. She experienced fatigue at all times out of all proportion to what she was required to do.

*Physical Examination:* The patient was short-waisted and long-legged, fairly well built; her weight was about 145 pounds. The skin was normal. Body hair and pubic hair were normal in texture, growth and distribution. Posture and gait were normal. The head was well formed and the hair was abundant. There was no tenderness to pressure on head or face. The temporal arteries were not palpable. Hearing was normal. Eyebrows were normal and there was no puffiness of the lids. The pupils and eye movements were normal. The thyroid was not enlarged. The teeth were clean and in good condition, the upper ones markedly separated. Mouth, fauces and nasal passages showed nothing of interest. The lungs and heart were normal. Pulse rate was 75, and blood pressure was 100-55. The results of the examination of the abdomen were quite negative.

*Treatment:* On March 13, 1922, administration, by injection, was begun of one ampoule of Burroughs & Wellcome's infundin 0.5 cc. once a day for ten days. When the second ampoule of infundin was administered the headache had disappeared and the patient felt improved in every way. On March 23, when the tenth injection was made, the patient declared she was well and felt like doing her work. On April 19 she experienced a menstrual period, painless and without

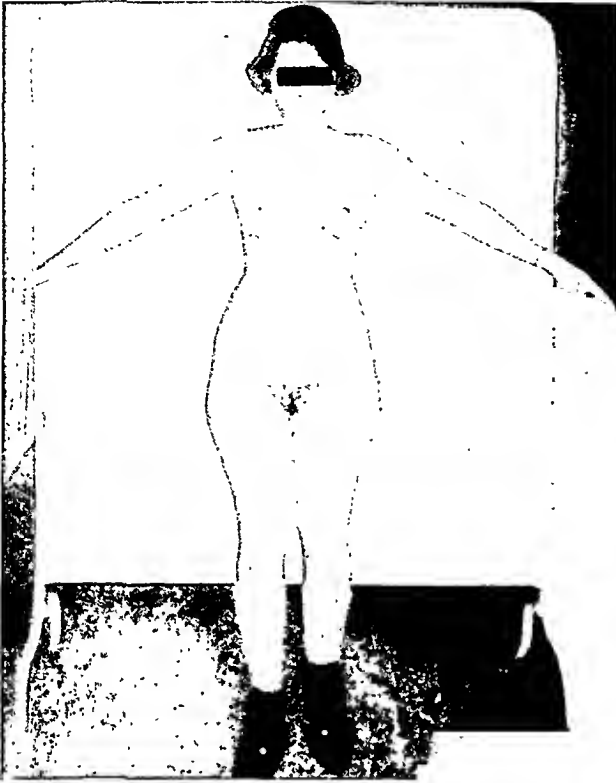


Fig. 4. Case II, M. R., definitely representative of the short-waisted, long-legged individuals who seem predisposed to confusing pluriglandular syndromes.



Fig. 5. Case II, M. R., showing posterior view which illustrates well the disproportion between body and trunk length and a type of adiposity common in pituitary patients.

headache. From March 23 to May 2, the patient received infundin three times a week for one week and then twice a week for one week. On May 2 the patient reported menstruation a week delayed. A headache and severe backache had lasted all night preceding the flow, but vanished when the flow appeared. July 17, 1922, the patient reported having menstruated in June, nine days late, but with no discomfort. She had remained free from headaches, felt well and continued to do her work. Treatment was discontinued.

She reported four times during the ensuing year. She menstruated regularly and remained free from headache up to June, 1926. During this interval the patient married, experienced a normal pregnancy and remained free from symptoms during gestation. Her reason for reporting in June, 1926, was amenorrhea following the pregnancy.

This patient was last heard from in 1928 and she was entirely symptom free. (Figs. 3, 4 and 5.)

**CASE III:** A. T., female, colored, married, age 21, was examined at the gynecological clinic of St. Luke's Hospital Dispensary, Chicago, November 6, 1921. The complaint was dysmenorrhea for the last year, during which time she had been unable to work, but had gained sixty pounds. She tired easily, felt

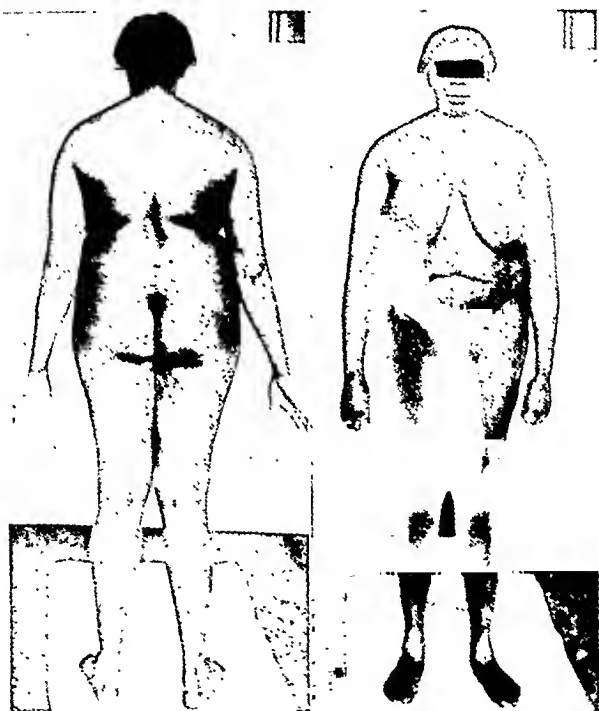


Fig. 6

Fig. 7

Fig. 6. Case III, A. T., exhibiting torso obesity, long legs, and short waist. This patient responded spectacularly to pituitary treatment.

Fig. 7. Case III, A. T., in whom the trunk disproportion connotes sexual repression and cyclic headache of pituitary type.

weak, and was short of breath on slight exertion. She was always thirsty, drank quantities of water, and habitually arose three times at night to urinate. The headaches were frequent, with onset in early morning. They caused a sense of fullness in the head and blurring of vision.

The patient had escaped all diseases of childhood. She attained her growth early, her height at fourteen years being 5 feet 6 inches.

**Physical Examination:** The patient was tall; the arms and legs were normal, but the trunk was disproportionately large. The head was rather small. The abdomen was fairly firm. Excessive fat about the abdomen hung in folds about the hips and over the mons. There was no supraclavicular padding. The



mammae were somewhat pendulous. There was a marked girdle of obesity extending down to about the middle or third of the femur. There was a transverse scar across the abdomen 18 cm. in length. The body hair was normally distributed and normal in texture. The gait was slightly waddling, but posture was erect and there was no lordosis. The pulse was normal, rate 90. Blood pressure was 140-70. Respiration was normal. Temperature was 99° F.

The head hair was black and kinky; there were no areas of alopecia. There was no tenderness to pressure on the head. The ears were normal. In the fundus of the left eye were seen several old hemorrhages below the disc in conjunction with one large and several small clumps of exudate. The right eye was normal. Face, mouth and teeth showed nothing abnormal. The neck was short, the thyroid normal in size. No pulsation was seen. The chest was well developed with good expansion. The heart and lungs were normal. The abdomen was pendulous; the old healed scar was in good condition. There was no evidence of abnormality in the abdominal organs. Examination showed Skeene's ducts enlarged, with a small cyst underneath the urethra. The uterus, ovaries, and tubes were not palpably diseased, but chronic salpingitis and adhesions were thought probable.

Roentgenogram showed the sella to be completely bridged. The pituitary fossa measured 1.2 cm., the floor somewhat thickened and depressed. The bones of the hands were unusually long, especially the metacarpals. No definite changes, such as rarefaction or osteosclerosis, could be seen in the bones.

*Treatment:* The routine treatment was instituted with the administration of ten consecutive daily injections of one ampoule of 0.5 cc. Burroughs & Wellcome's infundin, followed by similar injections three times a week for one week; then two times a week for one week; one injection the fourth week, then one in two weeks for a month, followed by an interval without treatment.

After an interval of one month without treatment the patient had lost 38 pounds in weight on August 13, 1923. Menstruation was regular and free from pain. November 12, 1923, she had gained 11 pounds. The headaches had not returned, but in order to see what influence pituitary therapy would have on the weight, infundin, 0.5 cc., was administered at three day intervals, until five doses had been given. On March 2, 1924, she was still free from headache. February 3, 1926, the headaches had not returned but she had again put on the 38 pounds she had previously lost in weight. Menstruation was regular and free from pain. (Figs 6 and 7.)

*CASE IV:* P. McC., female, white, married, age 41, was admitted to St. Luke's Hospital, Chicago, April 1, 1923.

*Complaint:* Headache and dysmenorrhea. The headache, more intense in the morning and almost continuous for the preceding ten years, becoming progressively worse, had been present most of the patient's life. Preceding each menstrual period the symptoms were so intensified as to confine her to bed. Other attacks almost as severe were frequent between periods. They were more severe on alternate days, with almost constant pain and nausea. Frequent vomiting afforded temporary relief.

The patient had one child, whose birth was normal in every way. During her pregnancy in 1920, severe headaches confined her to bed once a week. Headaches were constant while she was in the hospital after the child's birth. The patient's mother, who was subject to similar headaches, had experienced relief during pregnancy and had recovered at the age of 55. Her three sisters had headaches similar in type. The patient's menses began at the age of twelve, were quite painless for two years, regular and of the twenty-eight day type, with a moderate flow for seven days. Since the age of 14 dysmenorrhea had been present. She had leucorrhea for about five days subsequent to menstruation.

The patient said she had pleurisy on the right side at the age of fifteen, and at eighteen had a gastric ulcer. At the present time she experienced occasional pain in the stomach. She seldom drank tea or coffee. She was slightly constipated, used cathartics occasionally. She slept well. About twelve years prior to examination, the patient had begun to take headache medicine. Aspirin, dissolved in strong coffee, helped her most. Her family physician gave her a prescription of acetanilid, which had been taken in 20 grain doses daily for the preceding two years. She said she often took 80 or even 120 grains a day. For three years she had been given hypodermic injections of about one-half grain morphin at menstruation time. This treatment mitigated but did not terminate the attacks.

*Physical Examination:* The patient, though not acutely ill, looked tired, undernourished, and resembled a chronic sufferer. The skin and scalp were

normal. Vision was corrected for marked hyperopia and astigmatism. The eye muscles, pupils, ears, nose, teeth, and tongue were normal. The tonsils were small and atrophic; the pharynx was normal; the thyroid was small; there was no cervical adenopathy or rigidity. The breasts were small and atrophic, otherwise normal. The chest wall was thin and poorly muscled. Heart, pulse, and lungs were normal. Blood pressure was 94-68. The superficial vessels were not fibrosed. There was no capillary pulsation, edema, or venous engorgement.

The abdomen was flat, thin-walled, and poorly muscled; the abdominal organs were apparently normal. There was little subcutaneous fat on the extremities, which were otherwise normal. Deep reflexes were normal. There was no curvature of the spine, and no tenderness or rigidity of the back.

Roentgenogram showed normal sella, although the dorsum sellae arched forward nearly to the anterior clinoids. There were no cranial markings that would indicate disease. The blood showed: erythrocytes, 3,820,000; leukocytes, 9,400; hemoglobin, 77 per cent. Specific gravity of the urine was 1.020.

*Treatment:* One month prior to hospital admission the patient had been given six peptone injections, 1 cc. each, without effect on the headaches. As the patient's mother had been free from headaches during pregnancy, it was thought that the presence of foreign proteins might have been responsible. On admission to the hospital, April 1, 1923, the patient was given daily 0.5 cc. of Burroughs and Wellcome's infundin, intramuscularly. On the eighth day the patient complained of a slight headache. On the ninth day menstruation began with much less than the usual discomfort. The patient was discharged on the seventeenth day.

Medication was continued with the administration of 0.5 cc. ampoules of Burroughs & Wellcome's infundin daily for three days before the onset of menstruation. In November, 1923, despite occasional setbacks, she was still enthusiastic and grateful. A year later she reported having experienced only one headache during the menstrual month and sometimes escaped even that.

She continued taking the pituitary injections a few days before the menstrual period and at other times if she felt a headache coming on. In June, 1926, she was still in good health and she remained free from symptoms in 1929.

**CASE V:** J. J., female, white, married, age 26. Dispensary patient, January 15, 1923.

*Complaint:* Palpitation and shortness of breath for ten or twelve years; continuous headache for preceding three weeks. The palpitation, which occurred in paroxysms, often at night, and might be induced by worry or fright at any time, produced a pulse rate of 150 or thereabout. The dyspnoea on exertion was worse after an attack of influenza, and had become progressively worse during a pregnancy, which terminated in November, 1922, with the birth of a child. She had been "nervous" for thirteen years, with the habit of biting lips and nails; she was readily excited and irritated. Her husband and baby "get on her nerves" and often, especially at menstrual periods, she could not bear to have them around.

During a previous pregnancy she gained fifteen pounds. Her weight then remained at 196 pounds until the present pregnancy. Headaches, migrainous in type, a week in duration, with remissions of seven days, were coincident with weight increase. Regular menstruation, re-established three months after the baby was born, was without pain but was ushered in with unusually severe headaches, irritability and severe exhaustion. Sexual life was fairly normal for the first nine months of the married life, later on was "just endured."

*Treatment:* Beginning November 23, 1924, 0.5 cc. of Burroughs & Wellcome's infundin was given hypodermically every day for ten days, followed in the usual manner with one injection three times a week for one week, twice a week for one week, once a week for one week, and then once in two weeks for a month, followed by an interval free of treatment. The headache disappeared after the initial injection and for the first time since the birth of her baby she was able to take long walks in the open air, and felt like doing her work. Headaches recurred, but in much less severe form, when she menstruated a month after treatment was begun, but when headache was present a single injection of pituitrin brought relief at once.

A few months later the patient was put on a diet of 1,400 calories and within a month she experienced a weight loss of 13 pounds. She felt better, slept better, was not so short of breath, and did not "feel all dragged out." The diet was then reduced to 1,100 calories but soon she felt weak and returned to 1,500 calories. She had no headache for three weeks, but experienced one attack of tachycardia. Thyroid was then given by mouth for the first time,  $\frac{1}{2}$  grain

each morning for a week. The menses came on during this week without a headache. There was a further weight reduction of six pounds. The thyroid dosage was then raised to 1 grain daily. The pulse rate was 80. The patient felt greatly improved and menstruated for three consecutive times without a headache. However, after four months of freedom from headaches, she began to experience nightly attacks of palpitation, and this was an annoying complication for about two months, when she began to have alternate attacks of palpitation and headache preceding the menstrual period. During the attacks of palpitation thyroid was discontinued, as it was thought that the thyroid medication was a possible cause of bringing on the tachycardia.

The palpitation continued for a few months when it suddenly disappeared. Thyroid was again instituted and the palpitation did not return.

Over a period of six months treatment the patient had lost 54 pounds in weight. She remained free from headache for two years. For one year, she continued to receive the pituitary extract injections daily for three days before onset of menstrual period. The last year she had received no medication and had remained free from symptoms.

The patient was free from symptoms when last heard from in 1929.

#### SUMMARY

1. Pituitary headache occurs only in women. We have never observed in men any type of headache that is in the least amenable to pituitary therapy.

2. Pituitary extract, by injection, is the only effectual remedy. Pituitrin, by mouth alone, has failed to give satisfactory results. Pluriglandular therapy is of no avail. The use of thyroid extract is contraindicated.

3. The characteristic menstrual dyscrasias associated with pituitary headache are subject to incidental correction by means of pituitary therapy administered for relief of headache. They require no direct attention.

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# HUMORAL MECHANISMS CONCERNED IN OVULATION IN THE RABBIT

MAURICE H. FRIEDMAN

From the Department of Physiology, University of Pennsylvania Medical School,  
PHILADELPHIA

The female of most mammalian species exhibits a definitely regular rhythm in ovarian activity in which ovulation is an incident. It has long been accepted that the cyclic variations in the ovary and in the accessory reproductive organs are effected by some hormonal influences, although the identity of the hormones was not known. Even today one could not say definitely what these hormones are. Yet, as a result of the stimulating researches of Smith and Engle (19), and Zondek and Ascheim (21), as well as the works which these researches provoked, it has become increasingly apparent that one must consider the anterior lobe of the hypophysis among those elemental forces that pulse the rhythms in the generative system of the female.

There are some animals, however, that do not exhibit rhythmic ovarian activity; of these the rabbit is one. In the mature female of this species there is no periodic recurrence of heat, and similarly, no such recurrence of those ovarian changes which culminate in ovulation. The rabbit does not ovulate spontaneously, but only after coitus. At any time of the year, in an entirely unpredictable manner, the follicles in the ovary of an unmated female may develop to maturity. In such state they remain, apparently unchanged until the act of coitus releases those changes which result in ovulation some ten hours later. Because of this state of affairs, it was thought that the process of ovulation in the rabbit differed markedly from that in other animals. Thus, Heape (9) considered it extremely probable, "on the basis of observations made on the nerves of the ovary," that the discharge of the ova was effected by the stimulation of some erectile tissue in the ovary. Similarly, Marshall (14) considered the phenomenon reflex in nature. In his opinion the evidence pointed to the conclusion that "the discharge of the follicles occurs in response to a stimulus conveyed to the ovary by its nerves."

Recent studies have made such views untenable.

## EVIDENCE FOR THE PRESENCE OF A HUMORAL MECHANISM FOR OVULATION IN THE RABBIT

In 1929 a series of ovarian autotransplantations was performed on rabbits (Friedman, 5). In a single operation both ovaries were completely excised, and a few small pieces of ovarian tissue were placed in a canal in the rectus abdominis muscle. Shortly afterwards repeated attempts were made to mate these females. From five to seventeen weeks after the

operation thirteen of the fifteen females so prepared accepted coitus. At autopsy, 48 hours after coitus, large, blood-filled vesicles were found in the rectus muscle at the site of the transplant. Upon histological examination these blood-filled vesicles (Fig. 1) proved to be corpora hemorrhagica with

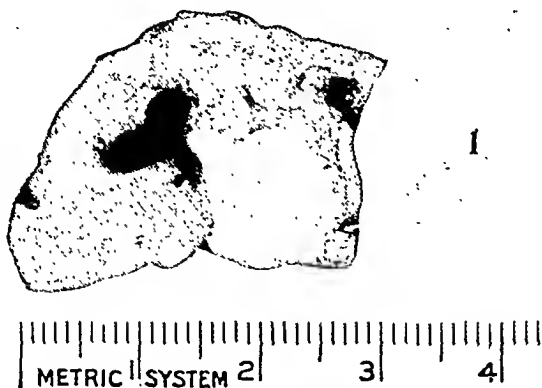


Fig. 1. Photograph of rectus muscle showing two corpora hemorrhagica protruding from the transplant.

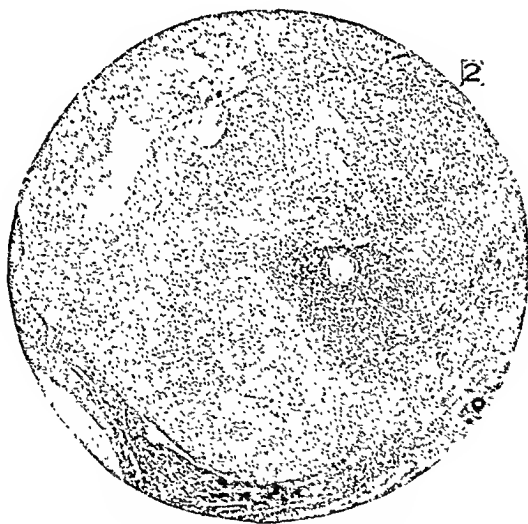


Fig. 2. Microphotograph of a section through a corpus hemorrhagicum showing the retained ovum.

retained ova (Fig. 2).<sup>\*</sup> In addition to these corpora hemorrhagica, genuine fresh corpora lutea were found in the transplants in two instances. In one animal which showed such corpus luteum (Fig. 3) the recently discharged egg was found in the tissue about the transplant (Fig. 4). On the basis of such evidence it was concluded that ovulation in the rabbit may occur without the participation of the ovarian nerves.

<sup>\*</sup>The figures in this paper have been previously published as illustrations of articles in the American Journal of Physiology.

Since these results were published I have encountered an earlier experiment which lends support to the results I obtained. In 1900 Knauer (12) performed a large number of experiments on dogs, cats and rabbits to

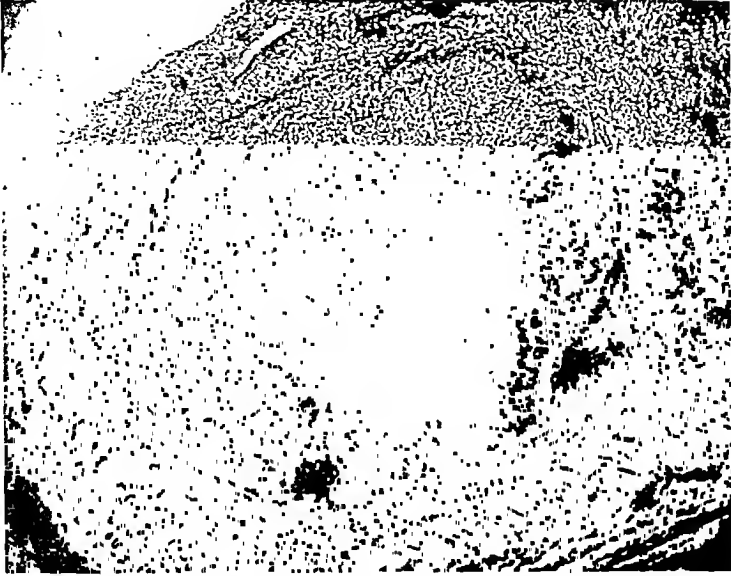


Fig. 3. Microphotograph of a section through the equator of a corpus luteum in the transplant of an animal 20 hours after coitus. Transplantation performed five weeks previously.



Fig. 4. Microphotograph of a section through the same corpus luteum ventral to the equator showing the recently discharged ovum (arrow).

demonstrate the adequacy of ovarian transplants in preventing uterine atrophy. Among the experiments on rabbits is a record of a successful ovarian transplant to the broad ligament. In a subsequent operation on

the same animal to inspect the condition of the uterus, the infundibulum of the fallopian tube was approximated to the ovarian graft and anchored there. Upon recovery from this operation the female was placed with a male. A month later she dropped a litter of normal young to bear testimony that ovulation may occur in ovarian transplants.

Yet, granting that some humoral change, or changes, are responsible for ovulation in the rabbit as well as in animals which ovulate spontaneously, one immediately asks as to the nature of these changes. Fortunately, there appeared almost simultaneously three reports which permit the presentation of a plausible hypothesis. Fee and Parkes (4) published some experiments in 1929 in which ovulation in the rabbit was prevented by an acute hypophysectomy within one hour after coitus. A similar operation performed later than one hour post coitum failed to prevent ovulation. Shortly after the experiments of Fee and Parkes, ovulation in the rabbit was produced by a single intravenous injection of an extract of the anterior lobe of the pituitary (Bellerby, 1), and by the single intravenous injection of whole urine from a pregnant woman (Friedman, 6). In these experiments the interval between the time of injection and ovulation was about ten hours, a time interval equal to that between coitus and ovulation. The work of Bellerby and of Friedman has since been confirmed by Jares, in Corner's laboratory (11), and by Hill and Parkes (10).

From these several researches it seems quite probable that in the rabbit the act of coitus stimulates the pituitary gland to discharge some hormone (or hormones) which, acting on the ripe follicles in the ovary, produces those changes which result in ovulation.

#### DISCUSSION

Regardless of the plausibility of the hypothesis that has just been presented, it is necessary to call attention to the objections that have been raised against some of the evidence upon which the hypothesis rests. From more than one source has come the criticism that the assumption that the substances in the urine of pregnant women and in the extracts prepared from the hypophysis are really anterior lobe hormones. Bellerby, Hill and Parkes (10) were unable to obtain ovulation in ovariectomized, hypophysectomized rabbits by the injection of extracts from the anterior pituitary. They say, "These results throw some doubt on the gonad-stimulating substance obtainable from urine of pregnancy, and on the desirability of avoiding the current fallacy of testing such substances on animals with their own hypophysis intact." This criticism of Bellerby is entirely justified, insofar as most biological tests of such substances have been performed on animals in which the pituitary had been removed. Yet, the experimental evidence which prompted this criticism does not remove the possibility that the gonad-stimulating substance in pregnancy is an anterior lobe hormone. In the first place, the experiments of Hill and Parkes were performed on decerebrate rabbits, and the extracts of urine, not whole, untreated urine, were used.



When one considers the possibility that an extraction process might result in a product more toxic than the urine itself, it will certainly be conceded that it would be better to examine the material in question by testing it on animals in better condition than are most deerebrate rabbits.

The criticism offered by Hill and Parkes, however, is not the only one which would raise a question as to the identity of the potent material in the urine of pregnancy and in extracts of the pituitary. Engle calls attention to the fact that the results obtained by the subcutaneous injection of whole pregnant urine in the immature mouse or rat are not identical with the results obtained by the daily implantation of fresh pituitaries. While the implantation of the fresh glands leads to the maturation of follicles and ovulation, the subcutaneous injection of whole urine leads to the luteinization of follicles without ovulation. From such data, Engle (2)

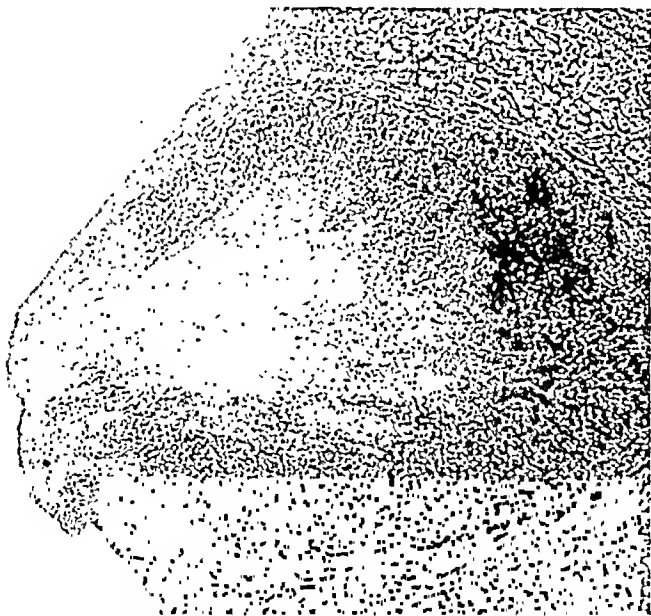


Fig. 5. Microphotograph of a section through a corpus luteum in the ovary of a rabbit 20 hours after a single intravenous injection of whole urine from a pregnant woman ( $\times 57$ ).

infers that, "If both the gonad-stimulating factor and the lutein producing factor are ascribed to the anterior lobe, then it must be assumed that there are two factors which act on the ovary, or that the same factor acts in a different manner in combination with the urine and as prepared in certain extracts, than when given in the fresh transplant." In a later paper (3) Engle voices the opinion that "It is difficult to consider the two types of response as being due to the same factor from the anterior lobe."

The evidence cited by Engle is not disputed. Nevertheless, his is not the only possible inference, as is attested by the results obtained by Bellerby and by Friedman. In the experiments of Bellerby (1) the single, intravenous injection of a hypophyseal extract provoked ovulation in the injected rabbits, although the subcutaneous injection of the same extract

resulted in the luteinization of follicles with retained ova. Similarly, in the experiments of Friedman (6), the single intravenous injection of urine from a pregnant woman was followed by ovulation in the injected rabbits (Fig. 5 and 6), while the repeated intraperitoneal injections of similar



Fig. 6. Microphotograph of a section through the fallopian tube of the same rabbit showing one of the discharged eggs.

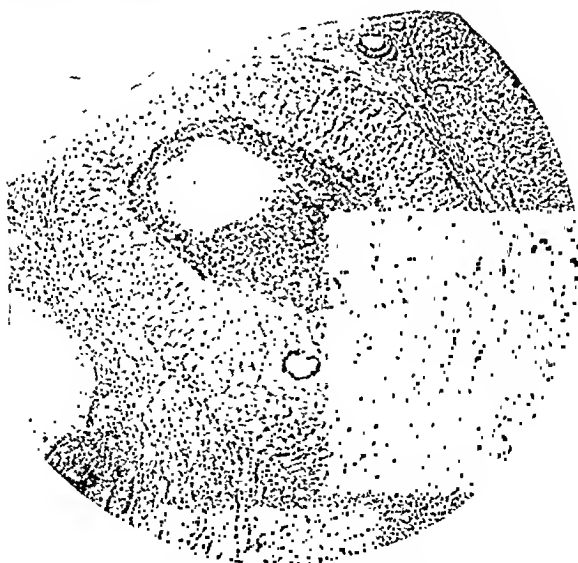


Fig. 7. Microphotograph ( $\times 43$ ) of a section through a partially luteinized corpus hemorrhagicum resulting from the repeated intraperitoneal injections of urine of pregnancy. The retained, degenerating ovum can be seen toward the base of the corpus hemorrhagicum.

urine produced the luteinization of follicles with retained ova (Fig. 7). Clearly, then, the mode of administration and the dosage must be considered as factors which are possibly responsible for variations in the response of the ovaries to the injection of any material.

Nor are these the only factors that must be given consideration. In the experience of Zondek the response of the immature mouse ovary to the injection of whole urine is highly variable, even when the age of the mice used is kept relatively constant, and the amount of urine injected and the route of administration kept uniform. It is just because of this variability in response that five mice are prescribed for the performance of each test for pregnancy by the Zondek-Aseheim method. Indeed in a given mouse the reaction of one ovary may be positive, while the response of the ovary on the opposite side is negative (20). In the rabbit, also, there are some variations in the ovarian response to a standard procedure which throw some interesting light on the question. During the course of over a hundred experiments for the diagnosis of early pregnancies (7), I most frequently noticed the formation of partially luteinized corpora hemorrhagica (with retained ova) in the rabbit ovaries. In some instances, however, fresh corpora lutea were seen, identical in every respect with the very early corpora lutea resulting from ovulation. Inasmuch as the route of injection in these experiments was constant, and the dosage of urine constant, we are left with only two variables to explain the variations in the response; namely, the concentration of the active substance in the urine samples, and the condition of the ovarian follicles at the time of the injections.

More striking than such results, however, was the finding in one of the animals used in the series for the diagnosis of pregnancy. In this animal one ovary contained several partially luteinized corpora hemorrhagica. In the other ovary were as many genuine, early corpora lutea. It is unfortunate that careful microscopic examination of the fallopian tubes of this rabbit was not carried out to prove without possible doubt that ovulation occurred in one ovary but not in the other. Nevertheless, the genuine, fresh corpora lutea in the one ovary seem sufficiently strong evidence for the probability of ovulation on one side, while the partially luteinized corpora hemorrhagica of the other ovary afford unquestionable evidence of the failure of ovulation on the other side. Rather than assume that one hormone acted exclusively on one ovary and that another hormone acted exclusively on the ovary of the opposite side, I should prefer to consider the possibility that purely local conditions in each ovary governed the response to the same substance or substances in the circulating blood.

Such variations in ovarian response to stimuli are found not only in the animal subjected to urine injections, but also in the normal animal. In the cyclic ovulation in rats it is not every one of a batch of apparently ripe follicles that responds normally to the ovulation-stimulating mechanism. Although ovulation occurs from most follicles, ovulation may not occur in others, the follicles forming corpora lutea with retained eggs (13). In the rabbit, too, there are instances in which the follicles do not all respond typically to the normal stimulus for ovulation. Not infrequently one finds, 24 to 48 hours after coitus, one or two corpora hemorrhagica

with retained ova in an ovary which contains several perfectly normal, fresh corpora lutea (8).

In view of these several types of evidence indicating that the ovarian response is determined not alone by the nature of the stimulus supplied, it seems the more cautious course to respect the possibility that the gonad-stimulating material in the urine of pregnant women may be an anterior lobe hormone. Recently, a new bit of evidence has been presented which supports this possibility. If one records the spontaneous contractions from the uterine fistula of an unanesthetized rabbit in heat, one usually sees fairly vigorous contractions. Within five to seven hours after coitus a similar recording will disclose only feeble activity if any at all. Before the tenth hour post coitum the uterine activity as recorded from the fistula is usually completely inhibited (15). It is important to note that this effect on the uterus is manifest before ovulation has occurred, and therefore cannot be a consequence of ovulation. With this in mind, it is particularly interesting to note that the decrease in uterine activity which follows the act of coitus can be exactly duplicated by the single intravenous injection of urine from a pregnant woman (16). Indeed, if one were to examine a series of tracings obtained over a ten-hour period from uterine fistulae in rabbits which had just copulated, and from the uterine fistulae of rabbits that had received the injection of an active urine, one could not possibly tell which was which. Just how the substance in the urine affects the uterine activity is not known; perhaps, through a direct action on the uterine musculature; perhaps, indirectly, through the ovaries or through some other intermediary. Nor is the identity of the inhibiting substance known. We are certain it is not folliculin, inasmuch as folliculin in the quantities contained in 5 cc. of urine from a pregnant woman has either no effect at all on the uterine activity (17) or a slight stimulating effect.\*

I believe it is probable that the ovulation inducing substance and the uterine inhibiting substance are the same. At present there is at hand no satisfactory evidence which would permit a more definite statement than that. Furthermore, we should hardly be justified in regarding the substances present in urine of pregnancy, and in hypophyseal extracts, as anterior lobe hormones. Although the evidence which prompted such criticisms as those of Engle, and of Hill and Parkes, is inadequate to exclude possibility, the evidence which can be marshalled for the identification of the substances in question as anterior lobe hormones is almost equally inadequate.

#### SUMMARY

1. It has been demonstrated that some humoral mechanism is concerned in ovulation in the rabbit just as it is in animals which ovulate spontaneously.

\*We have not concerned ourselves with any other substances which might possibly be derived from the pituitary and which might affect uterine activity, such as the oxytocic substances, inasmuch as there is not available evidence indicating their presence in the urine of pregnancy. Moreover, such substances have a fleeting, stimulating effect on uterine activity (18).

2. Ovulation in the unmated rabbit can be provoked by a single intravenous injection of an extract of the hypophysis, as shown by Bellerby, or by the single intravenous injection of whole urine from a pregnant woman.

3. The subcutaneous injection of such extract, or the repeated intraperitoneal or repeated intravenous injections of whole urine from a pregnant woman usually result in luteinization of follicles without ovulation.

4. The response of the ovary to the normal stimulus for ovulation, as well as to the substances obtained from the extraction of the anterior lobe and to the urine of pregnancy, is dependent not only upon the condition of the follicles at the time the stimulus is applied, but also upon the manner of administration of the potent substances constituting the stimulus, and upon the dosage of these substances. Therefore it seems unwise to draw any conclusions as to the nature of these potent substances, or as to the existence of one, or two, or more substances merely on the basis of the type of ovarian response elicited until the variable factors we have mentioned have been adequately and carefully controlled.

5. Finally, it appears very suggestive that the response of the rabbit ovary, and of the rabbit uterus, to those changes which are the consequence of coitus can be so exactly duplicated by the single intravenous injection of urine from a pregnant woman.

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# THE ROLE OF THE POSTERIOR PITUITARY GLAND IN THE EXPERIMENTAL PRODUCTION OF ARTERIOSCLEROSIS\*

ROBERT C. MOEHLIG, M.D.

DETROIT, MICHIGAN

Periodically sufficient data accumulate to permit us to view certain unsolved problems from a new angle. Such a condition, I believe, now exists in the problem of arteriosclerosis. In this paper will be shown that the posterior pituitary gland secretion is an important factor in the experimental production of arteriosclerosis.

Experimental production of arteriosclerosis in rabbits has been accomplished by several workers using various sorts of diets high in fats or fat-like substances to produce these changes.

The relationship between the pituitary gland and carbohydrate and fat metabolism suggested that the pituitary secretion might be concerned in arteriosclerosis. Likewise the pressor effect of posterior lobe extract on the blood vessel wall was another consideration that suggested the use of this substance.

At present it is recognized that fat metabolism is linked with the production of arteriosclerosis. That an intimate relation exists between cholesterol and atheromatous changes in the blood vessels has been known for some time.

The importance of the suprarenal cortex in cholesterol metabolism is well known. Suprarenal cortex hyperplasia in arteriosclerosis, hypertension, and nephritis has been described by many writers. Goldzieher (1) says, "The intimate correlation between lipid metabolism, adrenal cortex, and atherosclerosis is striking, although its mechanism is far from being clear. The cholesterol disturbance in atherosclerosis and its relationship to the changes of the adrenals has closed the ring of evidence which seems to prove that adrenal hyperfunction is among the most important factors in atherosclerosis, which we believe is but one particular manifestation of genuine hypertension."

A consideration of the correlation between the pituitary and suprarenal glands is therefore desirable. In other articles (2) it was shown that the state of the pituitary is reflected or mirrored in the suprarenal cortex. This relationship of the pituitary and suprarenal cortex is one of the most definite in endocrinology. Aplastic states of the pituitary are accompanied by aplasia of the suprarenal cortex and conversely hyperplasia of the pituitary results in hyperplasia of the suprarenal cortex.

We were led to use posterior lobe extract by the work of Krogh (3). He concluded from his experiments that the posterior lobe secretes a sub-

\*This paper is based upon work carried out with the assistance of Eugene A. Osius, M.D. The details have been published by the joint authors elsewhere. Sincere appreciation is expressed to the technical staff of Harper Hospital laboratory for their enthusiastic cooperation.

stance in low concentration which maintains capillary tone. Its pharmacologic pressor effect on the (mesodermal) blood vessels is well known and was further argument for using this substance in the experiments.

#### EXPERIMENTAL ANIMALS

Observations were made upon four groups of rabbits. A control group consisted of 5 normal rabbits on a normal laboratory diet of hay, lettuce, vegetables, etc.

Group A consisted of 5 rabbits which were fed on a normal laboratory diet with the addition daily of 12 cc. of cottonseed oil and 4 gms. of anhydrous lanolin for each rabbit. This is the diet used by Shapiro (4); it contains a large amount of cholesterol.

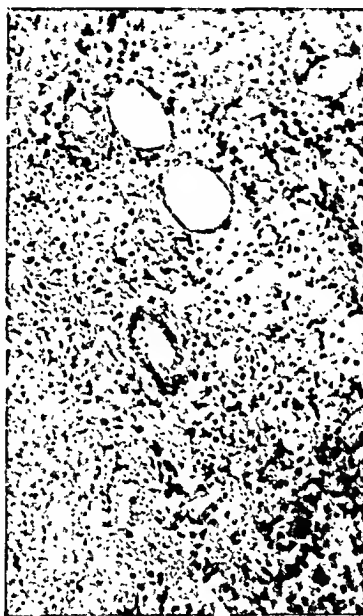


Fig. 1. Lipoidosis of Interstitial Tissue of Kidney. High Fat Diet plus Pituitrin.

Group B consisted of 10 rabbits which were placed on the same high fat diet as Group A and in addition received 1 cc. of obstetrical posterior lobe extract (Parke-Davis & Co. commercial pituitrin)\* injected either subcutaneously or intraperitoneally.

Group C consisted of 10 rabbits that were placed on a normal laboratory diet the same as the control group and in addition received daily 1 cc. of posterior lobe extract injected subcutaneously or intraperitoneally.

Blood cholesterol estimations, using Sackett's modification of Bloor's method (5), were made every ten days and the weights of the animals were taken at the same interval. The lanolin and cottonseed oil were heated and then poured onto the food. All animals were kept under the same conditions in the laboratory.

\*The pituitrin used in the experiments was kindly supplied by the Biological Department of Parke-Davis & Co. It was conveniently put up for us in specially prepared 30 cc. vials.

Except for a few areas of local irritation, the animals tolerated the injections of posterior lobe extract very well.

The first week we gave the injections twice a day and, following this, once a day over a period of one hundred days so that the average amount injected was 107 cc. of posterior lobe extract.

We began sacrificing the animals on the hundredth day of the experiment, by injecting air into the anrieular vein. Immediate autopsy was performed. Only some of the more important details will be given.

The fur of the animals on the high fat diet as well as those on the high fat diet and posterior lobe injections, became and remained more ruffled and shaggy than normal, the appearance of the animals' coats bearing a strong resemblance to that of the guinea pig during anaphylactic shock.

#### EFFECTS IN THE SUPRARENAL GLANDS

The actual suprarenal weights as well as the ratios of suprarenal to body weights are presented in tabular form.

##### Average Suprarenal Weights

Control Group (Normal Diet).....	278 mgms.
Group C. (Normal diet plus posterior lobe injections).....	415 mgms.
Group A. (High fat diet only).....	435 mgms.
Group B. (High fat diet plus posterior lobe injections).....	639 mgms.

##### Suprarenal weight—Body weight Indexes (Mgm.: 100 gm.)

Control Group .....	Average index 22.9
Group C. (Normal Diet plus Injections).....	Average index 27.5
Group A. (High Fat Diet).....	Average index 28.5
Group B. (High Fat Diet plus Injections).....	Average index 54.8

It is interesting to note in relation to the problem of arteriosclerosis that the suprarenal weights of the injected groups are much higher than the non-injected groups. Microscopic examination of the suprarenals showed that increase was confined to the cortex, the medulla being normal.

#### EFFECTS IN THE AORTA

Control Group: Not one of the control group showed the least suggestion of arteriosclerosis.

Group A: (High Fat Diet). Four of the five aortas showed macroscopic arteriosclerotic changes. Illustrative of this is the following as reported by the pathologist, Dr. Plinn F. Morse: The "aorta shows a few pin-point whitish plaques and over the surface are scattered irregular shaped areas of whitish density producing a somewhat mottled appearance. There is some increase of fat beneath the intima at the exits of the vessels." These observations confirm the work of others that the high fat diet alone produces arteriosclerosis.



Group B on a high fat diet plus injections of posterior lobe extract showed the most intense lesions of all. Eight of the ten surviving animals showed arteriosclerosis. The following report by the pathologist illustrates

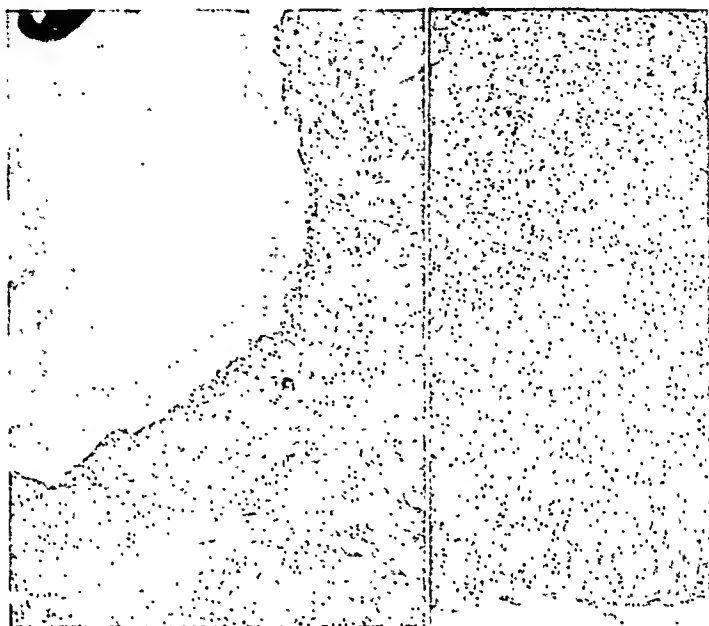


Fig. 2

Fig. 3

Fig. 2. Coronary Sclerosis. High Fat Diet plus Pituitrin.

Fig. 3. High Fat Diet plus Pituitrin. Showing Suprarenal Cortex Hypertrophy, Lipoidosis and Exhaustion Appearance of Cells.

the intensity of the lesions: There are "extensive linear and nodular atheromata distributed densely throughout the course of the aorta, as well as plaques varying in size from several mm. to pin point around the inter-



Fig. 4. Abdom. Aorta. Rabbit on High Fat Diet plus Pituitrin. Showing Arteriosclerosis.

costal arteries." Not all of this group showed such extensive involvement as that described, but unquestionably this group showed the most extensive lesions.

Group C on a normal diet and posterior lobe extract injections showed the following results: Six of the ten aortas were reported as macroscopically normal; four showed changes suggestive of early arteriosclerosis. These changes were not comparable to those in Group A on high fat diet alone. The pathologist described one of the aortas as "essentially a normal vessel except for diffuse indistinct whitish areas at the cephalic end." The average suprarenal weight of this group C was almost as much as the high fat group, being only 20 mgm. less than the latter. The average suprarenal index was only 1 less than the average of the high fat group.

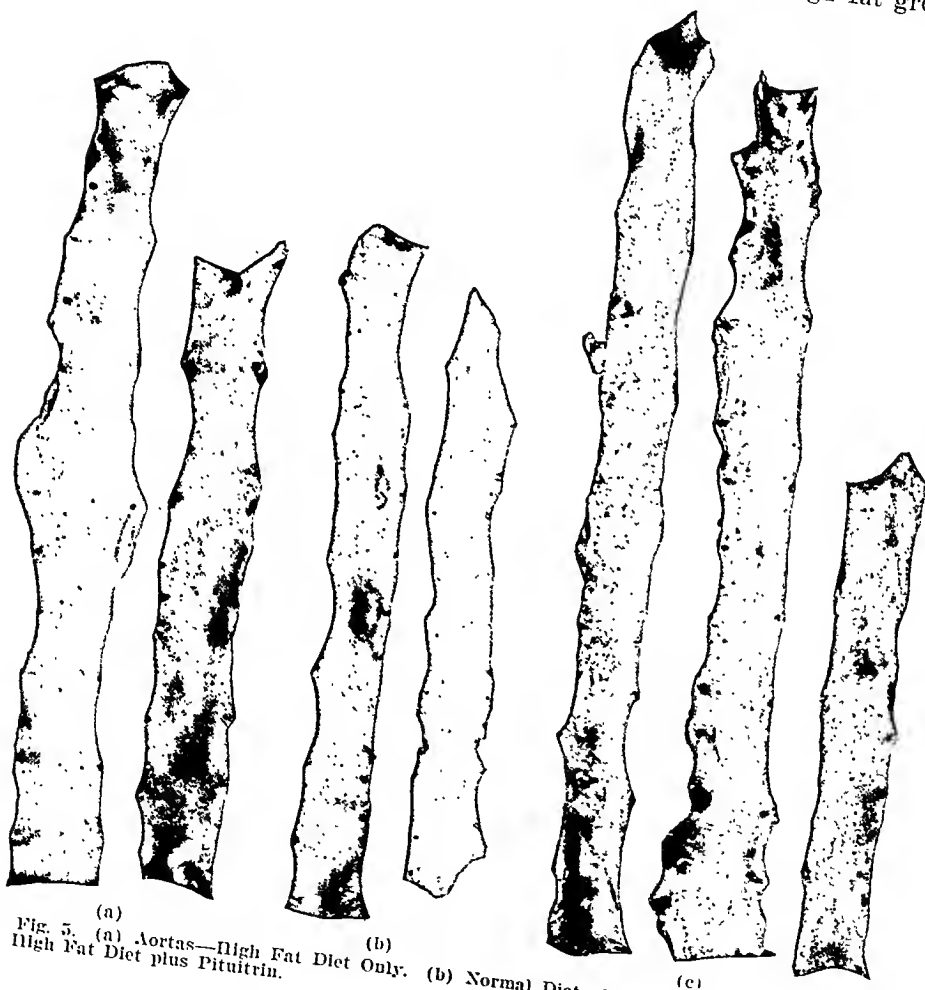


Fig. 5. (a) Aortas—High Fat Diet Only. (b) Normal Diet plus Pituitrin. (c) High Fat Diet plus Posterior Lobe Extract.

#### DISCUSSION

In previous articles (2) we have discussed at length the special relationship of the pituitary to those tissues that arise from the mesoderm. The importance of suprarenal cortex hypertrophy in arteriosclerosis, hypertension, and nephritis makes the suprarenal cortex hypertrophy found in

our injected animals of great significance. By the injection of posterior lobe extract alone, without the influence of diet, we are able to produce a suprarenal cortex hypertrophy, an important link in the chain of arteriosclerosis. The embryohormonic relations of the pituitary to mesodermal tissues furnishes the most reasonable conception of the problem.

#### SUMMARY

(1) Two groups of ten rabbits each were treated with high fat diet or this with pituitrin injections. Two control groups were fed on normal diet and of these one received pituitrin.

(2) Either fat diet alone or pituitrin injections alone caused hypertrophy of the suprarenal cortex. The two in combination caused a notably greater hypertrophy.

(3) Similarly marked arteriosclerotic changes were noted in the aortas of those rabbits receiving combined fat and pituitrin treatment. Lesser degrees of involvement were noted following either treatment singly.

(4) The embryohormonic relation of the pituitary to mesodermal tissues is offered as a reasonable explanation of the relationships shown.

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# THE EFFECT OF CHOLECYSTOKININ ON THE HUMAN GALL BLADDER

A. C. IVY, G. E. DREWYER\* AND B. H. ORNDOFF

From the Department of Physiology and Pharmacology, Northwestern University Medical School.

CHICAGO

In previous studies (1) (2) (3) (4) the following observations have been made: (a) The upper intestinal mucosa can be extracted so as to yield a product which on intravenous injection causes the gall bladder of the dog and cat to contract and evacuate. (b) The contraction of the gall bladder in dogs has been observed visually and moving pictures have been made. (c) The contraction and evacuation of the gall bladder is due to the effect of a specific substance, since it has been shown not to be due to a change in liver volume, a change in blood pressure, or contraction of adjacent structures, and since the active principle can be extracted only from the intestinal and gastric mucosa. (d) In cross-circulation experiments it has been shown that acid placed into the duodenum of one animal not only caused the gall bladder of that animal to contract, but about eight minutes later caused the gall bladder of the second animal to contract. These observations lead us to conclude that a hormone mechanism was concerned in gall bladder contraction and evacuation.

It was thought important to extend these observations to the human being. Before doing so it was necessary to demonstrate the existence of cholecystokinin in the intestinal mucosa of man, which has been done by Drewyer and Ivy (5) and to purify the active principle so that it could be injected intravenously into man without producing disturbances.

## THE PREPARATION OF A CHOLECYSTOKININ CONCENTRATE

In a previous communication, Ivy, Kloster, Lueth and Drewyer (3) reported a method for the preparation of cholecystokinin from the upper intestinal mucosa of the hog. The product was active in the dog in from 5 to 10 mgm. doses. The precipitation of cholecystokinin by trichloroacetic acid and its solubility properties in alcohol has been confirmed by Still (6).

We desire to report now an additional procedure which when applied to the above preparation uniformly yields a product active in approximately 3 mgm. doses in the dog—the product which we have used to study the effect of cholecystokinin on the human gall bladder.

*Methods of Preparation: The "1860" Method:* (a) One gram of "A pH 1802" powder (3) is dissolved in 30 cc. of water. (b) To this is added 70 cc. of absolute ethyl alcohol. The resulting solution is occasion-

\*Eli Lilly Fellow.

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ally cloudy. (e) To this solution is added from one to two volumes of absolute acetone (aldehyde free). The amount of acetone to be added varies with different batches of "A pH 1802" powder. One volume is first added and then mixed thoroughly by shaking. If a flocculent precipitate does not result, or if the precipitate formed goes into solution on shaking, a full or one-half volume more of acetone is added. The precipitate is impure and only a small amount of cholecystokinin is lost when two volumes of acetone are added. This impurity amounts to from one-half to two-thirds of the original weight of the "A pH 1802" powder. (d) The precipitate is removed by centrifuging. (e) To the filtrate is added five volumes of anhydrous ether (aldehyde free). A precipitate results which is allowed to form for one or two hours. The precipitate is collected by spinning and contains the activity. It is dried with a current of air and powdered. We call it "1860." It contains both secretin and cholecystokinin.

*The "1852" Method:* One gram of the "A pH 1802" powder is dissolved in 30 cc.  $H_2O$ . To this is added 70 cc. of absolute ethyl alcohol and 1 cc. of concentrated HCl. The resulting solution is occasionally cloudy. To this solution one volume of acetone is added. A flocculent precipitate results which we call "1851." This is removed by spinning and acetone is added to the filtrate ("1851" filtrate) to make a total of five volumes of acetone. The resulting precipitate, which is called "1852," contains some secretin and most of the cholecystokinin. It is collected by centrifuging and dried. Adding acetone to this filtrate up to ten volumes precipitates the remainder of the secretin, which is called "1854."

The method for assaying cholecystokinin previously described was used (Ivy and Oldberg, 1928).

*Results:* The "1860" method has been checked more than thirty times on six different batches of "A pH 1802" powder. In our hands it has uniformly yielded cholecystokinin in doses of from 2.0 to 3.5 mgm. in dogs weighing approximately thirty pounds, the smallest per kilogram dose being 0.05 mgm. per kgm. body weight. The recovery of cholecystokinin by this method is practically complete. A typical experiment is as follows: One gram of "A pH 1802" powder, which caused gall bladder contraction in 6 mgm. doses, was used. We obtained 0.505 mgm. of "1860" which was active in 3 mgm. doses. This particular product gave a pancreatic response in 1.4 mgm. doses, the original dosage in the "A pH 1802" powder being approximately 2.0 mgm. (See Table I).

Using the "1852" method, ten trials were made on three different batches of "A pH 1802" powder. On assay the milligram dosages necessary to cause a 1 cm. rise in intra-gall-bladder pressure were as follows: (1) 3.3, (2) 3.0, (3) 2.8, (4) 2.5, (5) 3.0, (6) 3.5, (7) 2.8, (8) 2.0, (9) 2.7, (10) 2.5. The "1854" precipitate when injected into dogs of approximately thirty pounds body weight causes the pancreas to secrete in 1.0 mgm. or less doses.

*Method of arriving at the dosage:* The response of the gall bladder of different dogs varies considerably. This variation, we believe, depends chiefly on the depth of the anesthesia and on the extent that the blood supply of the gall bladder has been disturbed. We keep on hand a number of different preparations of cholecystokinin, the activity of which is known. When a new preparation is to be tested, we first inject the "known" or control solution and in this way determine if the dog has a responsive gall bladder. If so, we then inject the "unknown" solution. We consider a rise of 1 cm. in intra-gall bladder pressure a threshold dose.

TABLE I.

## CHOLECYSTOKININ YIELDS USING THE "1860" METHOD.

Ten experiments in which complete record of yields was made.\*  
Hog material used.

Experiment No.	"A pH 1802" Powder	Dosage, mgm.	Weight "1860" Powder, mgm.	Dosage mgm.
1	1.000	6.0	0.505	3.0
2	1.000	6.0	0.470	3.8
3	1.000	7.0	0.465	3.0
4	1.000	7.0	0.468	3.1
5	1.000	6.0	0.470	3.0
6	1.000	8.0	0.275	2.8
7	1.000	8.0	0.272	3.0
8	1.000	6.0	0.456	3.4
9	1.000	6.0	0.405	2.5
10	1.000	6.0	0.426	2.9

\*Secretin dosages are not given. A better method for preparing secretin will be given in a following paper.

The variations in dosage are due to two factors, (a) the variation from dog-to-dog and other experimental factors beyond our control, and (b) the variation in purity of the product. We do not believe that our method will yield an absolutely uniform product, and claim only that it will vary within the limits given above.

Both our "1860" and "1852" products must be further purified before extensive human experiments are indicated. This product, however, is non-antigenic in the guinea pig and non-toxic in the dog. So we believed that a few experiments might be undertaken on human beings.

## EXPERIMENTS ON MAN

Five normal subjects (medical students) and three dispensary patients volunteered for the experiments.

The gall bladder was visualized with tetraiodophenolphthalein. From 25 to 30 mgm. of our product in aqueous solution (redistilled water and Berkefeld filtration) were injected at ten-minute intervals for one hour in the normal subjects and for one-half hour in the patients. X-ray pictures were made at 10 or 30-minute intervals.

In the first subject (L.A.C.) it was obviously necessary to experiment with the dosage. In this subject we failed to obtain definite evidence of emptying.

In the four normal subjects in which the above stated dosage was used, all manifested some degree of gall bladder evacuation with change in contour as was observed previously in dogs. In one (H.C.L.), the evacuation was complete; in the three others it was partial. Two of the five normal subjects felt "light-headed" from one-half to one hour after completion of the injections, which sensation disappeared within 30 minutes or one hour, no other symptoms being experienced.

The three patients in whom gall bladder disease had been suspected, but whose gall bladders visualized, received three doses at 10-minute inter-

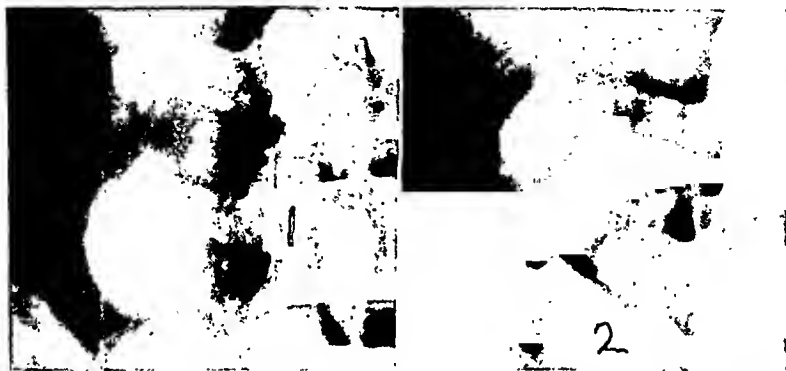


Figure 1. The gall bladder of a patient (man) with a pericholecystitis before (1) and after (2) the injection of three doses of cholecystokinin. Change in gall bladder becomes evident within five or ten minutes after the first injection. The second picture was taken about 45 minutes after the first.

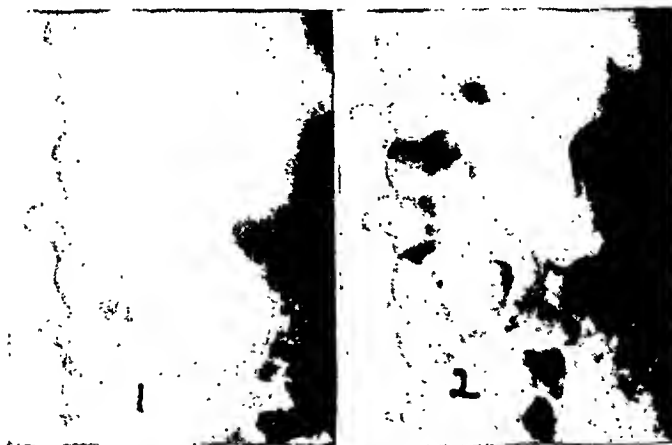


Figure 2. The gall bladder of a patient (woman) with suspected cholecystitis before (1) and after (2) the injection of three doses of cholecystokinin. The second picture was taken about 45 minutes after the first.

vals. Two of the three showed a definite decrease in the size of the gall bladder. One of the two had a peri-cholecystitis, which did not interfere with gall bladder evacuation, but was sufficient to cause symptoms. This patient about  $11\frac{1}{2}$  minutes after the second injection began to itch at various points as if he had been bitten by an insect and wheals appeared at the point of scratching. The itching and wheals disappeared within 3 minutes. This phenomenon occurred again after the third injection. The patient

who showed no emptying developed a chill about half an hour after the third injection. This patient complained of being "nervous" and chilly prior to the injection. We believe that the chill she had was probably due to the injection, although our normal subjects failed to manifest a similar reaction. This caused us to stop our work until a more highly purified preparation became available.

In our normal subjects a definite contraction or change in contour of the gall bladder was detectable in the "ten-minute" plate after the first injection, which was observed in dogs by Ivy and Oldberg.

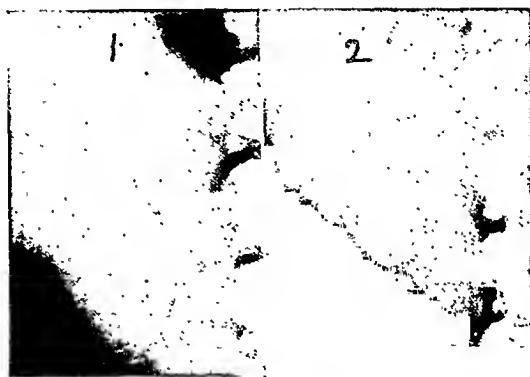


Figure 3. The gall bladder of a student (A.C.) before (1) and after (2) the injection of five doses of cholecystokinin at 10-minute intervals. Only partial evacuation occurred. Picture "one" was taken at 10:00 A. M. and "two" at 11:05 A. M.

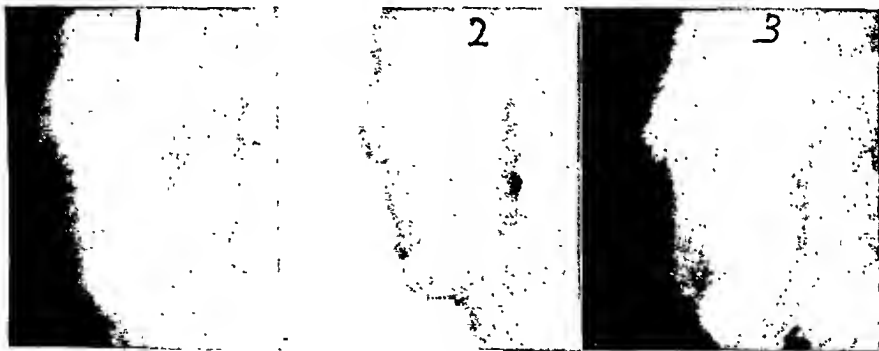


Figure 4. The gall bladder of a student (Hol.) before (1), during (2) and after (3) the injection of six doses of cholecystokinin. Picture "one" was taken at 10:00 A. M., "two" at 10:30 A. M., and "three" at 11:05 A. M.

#### DISCUSSION

This work raises the question of the therapeutic value of cholecystokinin. Since it is well established that egg yolk and cream by mouth lead to evacuation of the gall bladder within several hours, the authors doubt the therapeutic value of this active principle, in that cholecystokinin must be given intravenously and will do nothing apparently that egg yolk and cream will not do. All that can be claimed for cholecystokinin is that it does act more quickly, as might be expected.



This work does indicate in connection with the observations on dogs that a hormone mechanism for gall bladder contraction and evacuation exists in man.

#### CONCLUSION

1. The gall bladder of man can be caused to contract and evacuate on the intravenous injection of a "purified" extract of the upper intestinal mucosa, the active principle of which has been called cholecystokinin.

2. A method is described for preparing a cholecystokinin concentrate active in the dog in 3.0 to 1 mgm. doses, or 0.2 to 0.1 mgm. per kilo body weight, and non-antigenic in the guinea pig and non-toxic in the dog, but which produces an occasional reaction in man.

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# THE PLUMAGE AND OVIDUCT RESPONSE TO THE FEMALE HORMONE IN FOWLS\*

MARY JUHN, F. E. D'AMOUR, AND R. G. GUSTAVSON

Whitman Laboratory of Experimental Zoology and the Department of Physiological Chemistry, The University of Chicago.

We have reported in detail (Juhn and Gustavson, 1) the first observations on the assumption of female plumage by male fowls and the functional development of the oviduct of immature pullets subsequent to injections of female hormone prepared from human placenta.

Since, we have repeated these findings, with entirely comparable results with female hormone prepared from human pregnancy urine, using both the immature oviduct and the plumage as tests, and with female hormone prepared from cow placenta and with untreated human pregnancy urine, using the feathering alone as test.

These experiments, recorded here, thus further corroborate the original observations and extend the source for female hormone, effective in modifying the secondary sex characters of birds.

The biological observations were carried out as part of the program on the biology of sex now continued under the direction of Professor F. R. Lillie at the Whitman Laboratory of Experimental Zoology, the University of Chicago. The female hormone was prepared in the Department of Chemistry, the University of Denver and the Department of Physiological Chemistry, the University of Chicago.

The following procedure was used to prepare the hormone from cow placenta. The frozen material was ground in a meat grinder and treated with 1500 cc. of 95 per cent ethyl alcohol for every kilogram of placenta. After 48 hours the alcohol was filtered through a cloth and pressed out. The alcoholic filtrate was evaporated to a small volume and extracted three times with benzene. The benzene was removed by evaporation and the residue taken up with 70 per cent alcohol and extracted three times with one-fourth its volume of hexane. It is important that the 70 per cent alcohol should not contain more than 5 per cent solids. The 70 per cent alcoholic filtrate was then evaporated to dryness and the residue extracted with ether and 5 volumes of acetone added. The mixture was cooled to  $-10^{\circ}$  C. and allowed to stand at that temperature over night. The supernatant liquid was removed by filtration and the filtrate evaporated to dryness and taken up in olive oil.

The preparation from urine was made by the following method: Urine from pregnant women was made acid to Congo Red with acetic acid and extracted in a continuous extractor with ether. The ether was removed by

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evaporation and the residue dissolved in 5 per cent sodium hydroxide and again extracted with ether. This material was dissolved in olive oil.

All the female hormone preparations used were assayed in advance in rat units.

The birds belonged to the Whitman Laboratory stock of Light Brown Leghorns. This breed shows a pronounced plumage dimorphism, the feathering of the male and the gonadless bird is identical and differs from that of the female.

The response of the immature oviduct was studied in immature pullets. The hormone was injected over a given time and the test birds and their controls then autopsied and the weight and histological appearance of the treated and normal oviducts ascertained.

For the plumage changes, capons only were used in this series. The procedure was identical with the one employed previously and consisted in plucking feathers in definite regions and injecting the female hormone subcutaneously during the time of feather replacement, a period of about three to four weeks.

The records for each individual in both classes of birds included comb size and body weight during the experimental period, and in the case of the pullets a final autopsy with special reference to the condition of the ovary.

1. EXPERIMENTS WITH FEMALE HORMONE PREPARED FROM HUMAN PREGNANCY URINE. *Extract No. 1289, 40 rat units per cc.*

a. *Effects on the oviduct.* Pullet No. 358, age 115 days, was injected daily, subcutaneously, with 36 rat units, or approximately four rat units per 100 grams body weight for ten days. The total injected was 360 rat units.

Initial records, August 8, 1929, showed: Comb length, 3.1 cm.; comb depth, 1.3 cm.; body weight, 910 grams. Final records, August 17, 1929, showed: Comb length, 3.4 cm.; comb depth, 1.7 cm.; body weight 981 grams. On August 18, 1929, the pullet was autopsied. There was no inflammation at the sites of injection. The skin, muscle tissue and internal organs were all normal. The ovary was immature and the oviduct coiled and vascular. The weight was 1.5792 grams. Histological investigation showed the development in the treated duct of tubular glands and the muscle coat.

On the same date two control pullets of the same age and lot were autopsied. Pullet No. 317 showed: Comb length, 3.9 cm.; comb depth, 1.9 cm., and body weight, 967 grams. Pullet No. 343 showed: Comb length, 3.6 cm.; comb depth, 1.7 cm., and body weight 864 grams. The ovaries in both birds were in the immature stage. The oviducts of the two control pullets weighed 0.2959 grams and 0.3912 grams, respectively. Neither of the control oviducts showed the development of tubular glands or muscle layer.

*b. Effects on the plumage.* Capon 28-537 received subcutaneous injections of 88 rat units or 4 rat units per 100 grams body weight, daily, with the exception of Sundays, for about three weeks. Feathers were plucked the day before beginning injections, at intervals during, and two days after injections were interrupted. The records for the experimental period are compiled below:

Capon 28-537:

Date	Weight, gms.	Comb, cm.		
		L	D.	
8/ 8/29	2210	5.3	2.1	Feathers plucked, breast, saddle.
8/ 9/29				Injections begun.
8/15/29	2225	5.3	2.3	Feathers plucked, breast, saddle.
8/22/29	2288	5.5	2.3	Feathers plucked, breast, saddle.
8/27/29				Injections discontinued.
8/29/29	2334	5.5	2.5	Feathers plucked, breast, saddle.

The replacing plumage in the regions plucked the day before beginning injections was entirely female in breast and saddle. The one-day interruption of injections was recorded, exactly as noted in the earlier observations, by a black, male bar in the salmon, female, breast feathers. The saddle feathers remained unaffected by this diminution of hormone concentration as also noted previously. See Figures 4 and 8.

This differential sensitivity of the feathers in the breast and saddle to a diminution of female hormone concentration is correlated with the difference in growth rate present in the regenerating plumage in the two regions.

The incoming plumage in the regions plucked after the injections were interrupted was entirely male. See Figures 1 and 5.

The replacing plumage in the regions plucked after the injections were under way showed female tips and male bases. The proportion of female to male varied according to the length of time the regenerating feathers were under the influence of the female hormone and thus furnished a preliminary means of estimating the persistence of the hormone in the organism in concentrations effective in causing female plumage modifications. See Figures 2, 3, 6 and 7. This special question has since been further studied and a preliminary report of the experimental results published (Juhn, Faulkner and Gustavson, 2).

## 2. EXPERIMENTS WITH FEMALE HORMONE PREPARED FROM COW PLACENTAE. *Extract No. 1315, 50 rat units per cc.*

*Effects on the plumage.* Capon 29-986 received 110 rat units daily, or approximately 8 rat units per 100 grams body weight, subcutaneously, for 23 days.

It was found earlier that a positive response to the female hormone could be determined only after the time required—at least two weeks—for the plucked feathers to regenerate and pierce the sheath. More rapid readings seemed possible by allowing plumage regeneration to proceed for

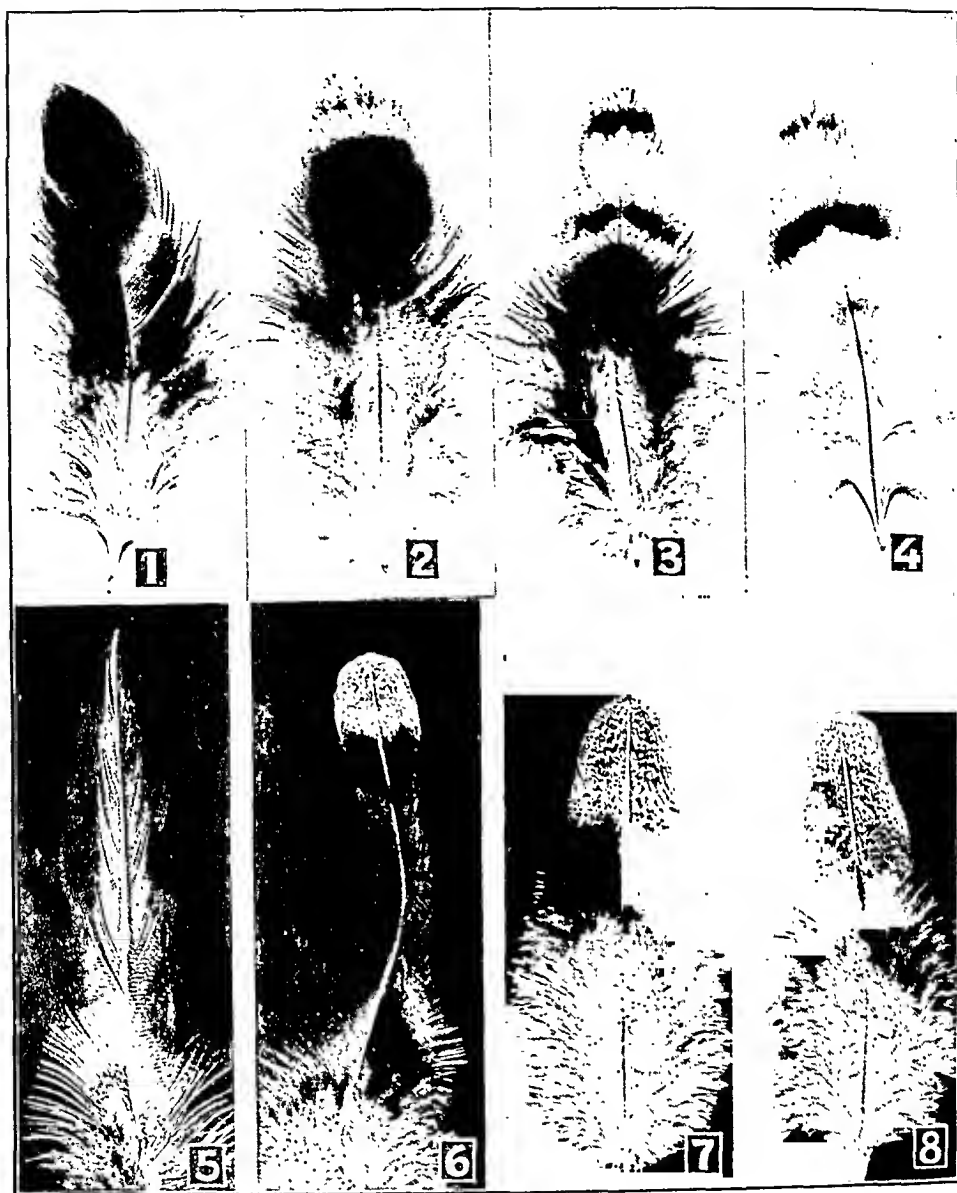


PLATE 1

## EXPLANATION OF FIGURES

Exp. 1. Capon 28-537. Female plumage modifications subsequent to injections of female hormone prepared from human pregnancy urine.

1. Male breast feather from region plucked after injections were discontinued.
2. Breast feather from region plucked towards end of period of injection showing narrow female tip and male base.
3. Breast feather from region plucked during first half of period of injections showing wide female tip and male base.
4. Entirely female breast feather from region plucked at the time of beginning injections. Note narrow black male bar recording one-day weekly interruption of injections.
5. Male saddle feather from region plucked after injections were discontinued.
6. Saddle feather from region plucked towards end of period of injection showing narrow female tip and long male base.
7. Saddle feather from region plucked during the first half of period of injections showing wide female tip and male base.
8. Entirely female saddle feather from region plucked at the time of beginning injections.

some time before beginning injections. Accordingly, feathers were plucked 14, 10 and 6 days before injections of the female hormone were started. The records are compiled below.

Capon 29-986:

Date	Weight, gms.	Comb, cm.		
		L.	D.	
10/10/29	1488	5.0	2.6	Feathers plucked, breast, saddle.
10/16/29	1531	5.0	2.6	Feathers plucked, breast, saddle.
10/21/29	1558	5.0	2.6	Feathers plucked, breast, saddle.
10/24/29	1558	5.1	2.4	Injections begun.
10/30/29	1624	5.1	2.6	
11/ 5/29	1672	5.1	2.5	
11/13/29	1733	5.0	2.6	
11/16/29	1722	5.1	2.6	Injections discontinued.
11/18/29	1762	5.1	2.6	Feathers plucked, breast, saddle.

The feathers in the regions plucked 14 and 10 days before beginning injections showed male tips and female bases; the feathers plucked 6 days before were entirely female. The incoming plumage in the regions plucked after injections were discontinued was entirely male.

The response to the female hormone was most rapidly ascertained, in about six days, in the breast feathers of the region plucked 14 days before the injections were begun. This observation was the basis for the development of a method permitting of more rapid readings yet, within 72 hours and with smaller quantities of the hormone (Juhn and Gustavson, 3).

### 3. EXPERIMENTS WITH HUMAN PREGNANCY URINE.

The material was filtered through a Berkefeld candle and kept in the ice-box. Just previous to injection the amount required was warmed to body temperature.

The effects on the plumage were studied in two adult capons, No. 29-939 and No. 29-984. Feathers were plucked in the breast only ten days before beginning injections. Each bird then received 40 cc. of the urine injected subcutaneously daily for 7 days. The amount was distributed in two doses of 20 cc. each administered in the morning and late afternoon, respectively.

The regenerating plumage showed distinct female modifications in the shape of a wide female bar in the male breast feather. There were no changes in the head-furnishings and while the injections caused some local irritation, the general condition of both capons continued good during the entire experimental period.

In conclusion it may be said that the female hormone prepared from human pregnancy urine, the untreated pregnancy urine as such and the female hormone prepared from cow placenta are equally effective in causing female plumage modifications in male fowls when administered in adequate dosages.

## SUMMARY

The effects of injections of female hormone prepared from cow placenta and human pregnancy urine on immature brown leghorn pullets and adult brown leghorn capons has been studied.

Hypertrophy of the oviduct takes place in the pullet, involving development of tubular glands and the muscle coat.

In adult capons feathers regenerating from plucked areas are of the female type during the period of injecting female hormone.

Failure to inject the birds one day a week is recorded by a bar of black (male) pigment in the breast feather, but the interruption of injections is not recorded in the saddle feathers.

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## STUDIES ON FAT METABOLISM

### II. THE EFFECT OF CERTAIN HORMONES ON FAT TRANSPORT\*

H. R. RONY AND T. T. CHING

From the Department of Physiology and Pharmacology, Northwestern  
University Medical School  
CHICAGO

In the preceding paper (1) of this series a preliminary investigation of the lipemia resulting from the ingestion of a fat test-meal in normal and obese subjects was made. A study of the "fat tolerance" and "sugar tolerance" of the obese subjects indicated that a correlation existed, which suggested along with other evidence the view that either insulin or the mechanism controlling carbohydrate mobilization promotes the deposition of tissue fat when fat is absorbed.

This study was undertaken to determine in dogs the effect of starvation, sugar feeding, insulin, pituitrin, and epinephrin on the blood fat curve following the ingestion of a test-meal of fat.

*Methods:* Adult dogs weighing from thirty to forty pounds were used. The fat meal consisted of 2 cc. of olive oil per pound weight given by stomach tube. Venous blood was removed (8-10 cc.) before and at certain intervals after the meal and the plasma analyzed for total fatty acids and cholesterol by Bloor's new method (2).

*Starvation:* The relation of starvation to alimentary lipemia was studied because in starvation the carbohydrate reserve of the body is markedly reduced and fat is mobilized from the fat depots, which might be expected to modify the alimentary lipemia.

Considerable work has been done on the effect of starvation on the fat of various tissues, especially the liver, heart and muscle with variable results. The effect of starvation on blood fat is within the limits of normal variation (3). Bang (4), as a result of his work, stated that because of the effect of nutrition on alimentary lipemia, it is necessary to use starved dogs, a generalization which is indicated by our results.

In the first part of our work we gave the fat meal 15 hours after the preceding meal, no attention having been paid to the character of the last meal, the stock diet being bread, yellow corn meal, and bone soup. Most of the dogs responded with a definite increase in blood fat after the test-meal beginning about two hours after and lasting from 10 to 12 hours. Some, however, showed little or no increase in blood fat which has been observed by other workers in this field. It was found that the marked variation can be eliminated by starving the animals several days (7-14 days) before the test. This was demonstrated by fat tolerance tests performed in the same

\*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 24, 1930.



animal in the fasting and well-fed condition. Water was allowed ad libitum. During the feeding period the dog was given all that he would eat twice daily.

Table I shows the results in four dogs which failed to show alimentary lipemia on 24-hour starvation or less.

TABLE I  
SHOWING EFFECT OF STARVATION ON ALIMENTARY LIPEMIA IN DOGS THAT FAILED TO MANIFEST LIPEMIA UNLESS STARVED

Dog	Lbs. Weight	Feeding Period	Starvation	Total Fatty Acids, mgm. %				
				Before	2 Hours	5 hours	7 hours	
10	35	7 days	16 hrs.	312	325	336	327	70 cc. olive oil each test.
			12 days	228	554	580	510	
			10 days	285	295	321		
12	34	10 days	13 days	382	494	610		
			24 hrs.	285	270	316		
21	36	7 days	7 days	305	488	560		
			17 hrs.	266	275	280		
13	33	4 days	16 hrs.	352	347	340		
			3 days	350	390	415		
			7 days	266	350	424		

The results show that after abundant feeding the "fat tolerance" is "high," and after fasting 3-13 days it is "low." The state of nutrition of the dog modifies the alimentary blood fat curve but does not materially affect the continuous blood fat level.

In most of the work described from now on in our paper the dogs were starved from one to two weeks before the test-meal of fat was administered.

*Sugar Administration:* Since the nutritional condition has an effect on the alimentary blood fat curve, it was considered significant to determine the effect of glucose administration on the blood fat curve.

Bang (4) found that the administration of bread (5 experiments) exercised a strong inhibitory effect on the alimentary lipemia in dogs and concluded that a liver rich in glycogen prevents fat from accumulating in the blood. McClure and Huntzinger (5) found that the ingestion of all types of food-stuffs in man causes an increase in blood fatty acids, carbohydrates causing the smallest.

TABLE II  
SHOWING THAT THE ORAL ADMINISTRATION OF GLUCOSE WITH THE FAT MEAL PREVENTS ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Total Fatty Acids, mgm. %		
		Before	After 2 Hours	After 5 Hours
114	8	259	275	285
115	10	219	210	221
116	10	345	354	350
118	7	316	318	325
119	13	326	340	322
*117	9	259	461	316

\*In this dog the glucose was given two hours after the olive oil.

In the experiments the gain of glucose per pound of body weight in 24 hours was given by stomach tube along with the olive oil or hypodermically or hypodermally with an alimentary lipemia on the administration. The results are shown in Table II.

It is quite evident from these experiments that the oral administration of glucose prevents or markedly reduces the alimentary lipemia.

Since the glucose was given by mouth the question arises as to whether or not the absorption of the fat was modified. For this reason it was deemed advisable to administer the glucose parenterally.

In three experiments glucose was administered intravenously. The results are shown in Table III.

TABLE III  
SHOWING THAT THE INTRAVENOUS ADMINISTRATION OF GLUCOSE PREVENTS ALIMENTARY LIPEMIA

Dog No.	Starvation Days	Procedure	Cholesterol %	Total Fatty Acid %
52	4	12:00—70 cc. olive oil by stomach tube.	0.188	0.300
		3:30—50 cc. 20% glucose intravenously.	0.111	0.182
		4:30	0.103	0.188
53	8	11:15—80 cc. olive oil by tube and 50 cc. of 20% glucose intravenously.	0.093	0.113
		1:30	0.110	0.119
		3:30	0.126	0.018
54	6	11:35—80 cc. olive oil by tube.	0.097	0.310
		1:30—50 cc. of 20% glucose intravenously.	0.093	0.013
		3:30	0.097	0.326
		4:25	0.092	0.323

In three other experiments glucose was given hypodermically (Table IV).

It appears from these experiments that the parenteral administration of glucose also prevents or reduces the alimentary lipemia.

*Insulin:* Macleod (6) found that insulin decreases the blood and liver fat in diabetic dogs. That insulin has a remarkable effect on diabetic lipemia has been repeatedly observed in the clinic [Joslin (7), Rabinowitch (8), Chauffard and Labbe (9), Fowden (10)].

TABLE IV  
SHOWING THAT THE SUBCUTANEOUS ADMINISTRATION OF GLUCOSE PREVENTS ALIMENTARY LIPEMIA

Dog No.	Starvation Days	Procedure	Cholesterol %	Fatty Acid Total %
60	5	10:00—50 cc. olive oil by tube and 500 cc. 10% glucose subcutaneously.	0.158	0.504
		1:15	0.151	0.534
		2:15	0.160	0.553
61	8	12:00—100 cc. olive oil by tube.	0.125	0.335
		2:30—500 cc. 10% glucose subcutaneously.	0.172	0.554
		4:00	0.172	0.480
61	10	10:30—50 cc. olive oil by stomach tube and 150 cc. 10% glucose subcutaneously.	0.135	0.425
		11:30—200 cc. 10% glucose subcutaneously.	0.161	0.445
		1:30	0.150	0.465
		3:00	0.155	0.485

Just how insulin brings about this change is not known. According to Chauffard and Labbe (9) insulin influences fat metabolism independently of its effect on carbohydrate metabolism. Wertheimer (11) finds that insulin prevents lipemia and fatty infiltration of the liver in phlorizin poisoning and causes the phlorizin lipemia to disappear and the fatty liver to return to normal. Dudley and Marrian (12), however, find that the amount of fatty acids in the liver was not changed in normal starved mice following insulin, which was confirmed by Raper and Smith (13). Wertheimer (11), Labbe and Tamalet (14) and Schmidt and Saatchian (15) report that insulin hypoglycemia is associated with decreased blood cholesterol, the latter observers finding that the fatty acids were affected more than cholesterol. White (16) reports a slight rise in blood fat after insulin. In this connection it is interesting to note that Shih-Hao and Mills (17) found that insulin decreases blood cholesterol and fat in nephrosis without materially affecting the blood sugar level, which indicates that insulin causes deposition or disappearance of blood fat irrespective of blood sugar level. Raper and Smith (13) conclude that fat synthesis in the liver is not associated with insulin hypoglycemia and believe that in the light of our present knowledge it is impossible to correlate changes occurring in blood fat with those occurring in the liver. But Bang (4) takes the position that the diabetic organism is more or less unable to deposit absorbed fat in the tissues, the liver being chiefly at fault.

Onohara (18), as far as we have been able to find, is the only one who has directly studied the effect of insulin on alimentary lipemia in normal dogs. He studied two dogs and found the lipemia to be reduced in one but not the other. He paid no attention to the nutritional state of the animals. Hartmann (19) found that in man the ingestion of 50 gm. of butter and 20 gm. of oatmeal caused a slight rise in blood fat at 1 hour which returned to normal in 4 hours. In his cases insulin caused a slight decrease in blood fat and did not modify to a significant degree the blood fat curve after the ingestion of his test-meal. It is to be noted that he used carbohydrate with fat in his test-meal.

We desired first to study the effect of insulin on the fasting blood fat level. In three dogs starved for seven or eight days, insulin sufficient to

TABLE V  
SHOWING THAT INSULIN PREVENTS ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Amount of Insulin Units	Total Fatty Acid, mgm. %		
			Before	2 Hours	5 Hours
102	8	20	305	314	310
103	10	30	289	268	304
105	7	25	410	425	432
106	14	25	324	316	318
107	10	30	194	176	205
108	12	40	343	340	338
109	8	30	259	...	270
110	11	25	415	428	402

lower the blood sugar to 0.038-0.024 gm. produced no changes in the fasting blood fat.

In eight other dogs we studied the effect of insulin on alimentary lipemia. In these experiments the dogs were fasted for from seven to fourteen days and the insulin was given hypodermically at the same time the fat meal was given. The results are shown in Table IV and demonstrate that insulin prevents alimentary lipemia in normal dogs that have been fasted.

*Epinephrin:* Alpern and Collazo (20) report that epinephrin depresses slightly the blood cholesterol and blood fat values. Fleisch (21) finds that intravenous epinephrin (0.1-1 mgm.) causes a slight decrease in blood fat and cholesterol, whereas given subcutaneously in larger doses (3-6 mgm.), it causes a marked increase of blood fat and cholesterol at the end of 24 hours. Jollson and Shoor (22) find that adrenalin has no effect on blood cholesterol in adrenalectomized dogs.

In the experiments shown in Table VI the effect of adrenalin was studied on the fasting blood fat level. No definite changes occurred in the blood fat or cholesterol.

TABLE VI  
SHOWING NO EFFECT OF EPINEPHRIN HYPODERMICALLY ON BLOOD FAT OF  
NORMAL FASTING DOG

Dog No.	Procedure	Time	Total Fatty Acid, %	Blood Sugar, %	Cholesterol %
2	Fasting 2 days. 3 mgm. adrenalin at 10:00.	10:00	0.554	0.089	0.258
		11:00	0.512	0.160	0.230
		12:00	0.548	0.142	0.210
		1:00	0.582	0.118	0.235
4	Fasting 2 days. 2.5 mgm. adrenalin at 10:00.	10:00	0.367	0.101	0.128
		11:00	0.349	0.230	0.117
		12:00	0.385	0.240	0.115
		1:00	0.338	0.247	0.107
		2:00	0.390	0.250	0.107
9	Fasting 5 days. 2.0 mgm. adrenalin at 12:00.	12:00	0.216		0.106
		2:00	0.234		0.073
		4:15	0.220		0.095
56	Fasting 24 hours. 4.5 mgm. adrenalin March 19th, 11:45. (March 20) (March 21)	11:45	0.726	0.087	0.133
		2:30	0.772	0.231	0.141
		10:00	0.692	0.092	0.173
		3:00	0.715		0.152
		3:00	0.526		0.241
58	Fasting 7 days. 5 mgm. adrenalin April 14, 11:00 A.M. (April 15) (April 16)	11:00	0.520		0.145
		11:00	0.507		0.147
		11:00	0.532		0.166

In further experiments the dogs were fasted and then given from 2 to 3 mgm. of epinephrin subcutaneously along with the fat meal. The results are shown in Table VII. The data obtained do not differ materially from the normal fat tolerance values obtained in fasting dogs not receiving epinephrin.

So epinephrin as administered had no effect on the alimentary lipemia of these dogs, nor on the fasting blood fat level.

TABLE VII  
SHOWING EFFECT OF EPINEPHRIN SUBCUTANEOUSLY ON ALIMENTARY LIPEMIA  
OLIVE OIL, 70 CC. AND ADRENALIN, 2-3 MGM. WERE ADMINISTERED

Dog No.	Fasting Days	Total Fatty Acids, mgm. %			
		Before	2 Hours	5 Hours	7 Hours
*114	8	401	510	770	609
*115	7	429	507	623	582
*116	12	354	416	563	429

\*Note response to glucose and fat in Table II.

*Insulin and Epinephrin:* The question arose whether epinephrin might not antagonize the action of insulin on blood fat, since it antagonizes the effect of insulin on blood sugar. This might not be predicted, however, since it was pointed out above in the discussion of the literature on the effect of insulin on blood fat that insulin caused deposition of fat irrespective of blood sugar level. The results are shown in Table VIII. The epinephrin did not antagonize the insulin action, although there was not sufficient epinephrin absorption to prevent the blood sugar from falling.

TABLE VIII  
SHOWING THAT AS THE EXPERIMENTS WERE PERFORMED EPINEPHRIN FAILED TO  
ANTAGONIZE THE EFFECT OF INSULIN ON ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Total Fatty Acids, mgm. %				Blood Sugar, Mgm. %	
		Before	3 Hours	4 Hours	5 or 7 Hours		
117	7	354	460	409	377	84-50	Insulin and epinephrin given at 3rd hour.
118	7	382	405		401		Insulin and epinephrin given with fat.
120	11	404	415		436		Given with fat.

Dosage insulin 25 units and epinephrin 3 mgm. intramuscularly.

*Pituitrin:* Coope and Chamberlain (23) found that the injection of pituitrin into rabbits caused a definite increase in the fat of the liver. Studies of blood fat were not made.

Our experiments were performed by injecting two ampules of (obstetrical) pituitrin intramuscularly at the same time the fat meal was given. The results are shown in Table IX.

TABLE IX  
SHOWING THAT PITUITRIN HAS NO EFFECT ON ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Total Fatty Acids, %		
		Before	3 Hours	5 Hours
72	7	0.520	0.636	0.713
73	8	0.381	0.520	0.595
118	8	0.410	0.533	0.605

The results show that the pituitrin had no appreciable effect on lipemia following the fat meal.

# DISCUSSION

After ingestion of fat there is a continuous absorption of the fat from the intestine into the blood stream, and simultaneously a continuous passage of the fat from the blood stream into the tissues. The alimentary lipemia curve represents the difference in the rate of these two processes. The alimentary lipemia curve may be compared with the alimentary glycemia curve which represents the difference between the rate of sugar absorption and sugar "utilization." "Sugar tolerance curves" are usually interpreted as expressing the rate of sugar "utilization." The rate of the passage of the fat into the blood stream after ingestion of fat, is, of course, a more complicated process, since it includes also the rate of the digestion of the fat, which depends on bile and pancreatic juice secretion, etc. Yet it is probably safe to say that under standard experimental conditions in the presence of normal digestive organs, the rate of the fat digestion and absorption is fairly uniform. With this precaution, alimentary lipemia curves may be considered as approximate measures of the rate of fat "utilization."

On this basis, our experiments indicate that insulin markedly promotes the passage of ingested fat from the blood stream into the tissues. If sufficient doses of insulin are given, all ingested fat passes from the blood stream without appreciably elevating the blood fat level at any moment. This is the more remarkable since insulin has no definite effect on the fasting blood fat level.

Does insulin promote the passage of the ingested fat from the blood stream by direct action, or is this effect of insulin secondary to its effect on carbohydrate metabolism? That the effect of insulin on the blood fat is not a consequence of the insulin hypoglycemia is evident from the fact that administration of sugar had the same effect in our experiments. These observations along with the failure of epinephrin hyperglycemia to prevent alimentary lipemia suggest strongly that the effect of insulin on alimentary lipemia is independent from its effect on the *blood sugar*. But at the same time it shows that the deposition of ingested fat is in some way dependent on carbohydrate metabolism. Apparently the type of carbohydrate metabolism going on in the *tissues* or in some specialized tissue such as the liver is the factor controlling the passage of ingested fat from the blood stream into the tissues; or it might be said that glycogen formation favors fat deposition.

It is worthwhile to recall at this juncture Wertheimer's findings on the effect of insulin on another phase of fat transport, namely, on fat mobilization in phlorizin poisoning. Wertheimer found that insulin inhibits the passage of fat from the fat depots into the blood and into the liver in phlorizin poisoning. He did not determine whether sugar admin-

istration has a similar effect. But it has been known for a long time, and was observed by Wertheimer also that in order to obtain marked fat accumulation in the liver and ketosis through phlorizin poisoning, the animals have to be starved for several days (24). Our experiments show that starvation also promotes the accumulation of the ingested fat in the blood. It seems, then, that starvation has the same effect on fat transport whether the transported fat is ingested fat or mobilized depot fat. Now, one of the chief changes in the body after brief starvation is a decrease in the carbohydrate reserve of the body which again suggests a dependence of fat transport on the carbohydrate metabolism of the tissues. This relation may be expressed in the following way: the promotion of carbohydrate synthesis and oxidation favors the fixation of fat in the peripheral tissues; a decrease of carbohydrate synthesis and oxidation promotes the accumulation of fat in the blood and liver.

#### SUMMARY AND CONCLUSION

1. It was shown experimentally in dogs that fasting augments and previous abundant feeding decreases alimentary lipemia.

2. The administration of glucose either by mouth or parenterally inhibited alimentary lipemia in fasting dogs.

3. Insulin and epinephrin had no definite effect on the fasting blood fat of dogs.

4. Insulin was found to inhibit alimentary lipemia.

5. Epinephrin and pituitrin had no definite influence on alimentary lipemia.

It was concluded that carbohydrate metabolism plays an important, if not essential role in the regulation of the blood fat level of normal dogs during the alimentary absorption of fat.

We desire to express our thanks to Dr. A. C. Ivy for his interest and advice.

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# Book Reviews

THE NEW CRIMINOLOGY. Max Schlapp and Edward H. Smith. 1928. Boni and Liveright, N. Y. Pp. 325.

This volume is a combination of interesting sociology, fair psychology, poor psychiatry and incredibly bad endocrinology. In a sentence, the burden of the book is that criminality is due to hormone imbalance in the mother during gestation of the future criminal.

L'HYPOPHYSE. H. Penan, L. Blanchard and H. Simonnet. Les Presses Universitaires de France, Paris, 1929.

L'hypophyse is a complete summary, in French, of the most important investigations upon the hypophysis carried out, prior to 1928, in France, Germany, England and the United States. The literature reviewed in the book is listed in a carefully prepared bibliography containing titles of 575 papers and monographs. The authors are to be commended for the excellent way in which they have evaluated the experimental work reported by the various writers. The authors of L'hypophyse have prepared many tables and charts to aid the reader in understanding and grasping the significance of steps in the preparation of extracts and the results of tests on animals. Anatomy, histology, chemistry and pharmacology of the anterior and posterior lobes are covered in a thorough manner up to 1928. So much progress has been made in the last two years in the study of the anterior lobe that the book is already out of date in that phase.

Clinical applications of extracts of the hypophysis are not dealt with as the book is not intended for a physicians' manual. It is an excellent contribution to the scientific literature.

DIE PRAKTISCHE THERAPIE MIT HORMONEN UND VITAMINEN MIT BESONDERER BERÜCKSICHTIGUNG AKTUELLER ERNÄHRUNGSFRAGEN. Various authors. 1930. Otto Gmelin, München. Pp. 138.

Cited in Endokrinologie, 6: 234. 1930.

## Abstract Department

A tumor of the adrenal gland with fatal hypoglycemia. Anderson, H. B., Am. J. M. Sc. 180: 71. 1930.

A unique case is reported of a patient in which the only outstanding pathologic finding was a tumor of the left adrenal gland. There was also congestion of the pancreas and pituitary gland. The symptoms were for a time relieved by glucose administration, but later glucose failed to relieve the symptoms. Epinephrin was given one or two days before the patient died but without effect. When the blood sugar fell below 0.07 the patient became restless, confused mentally and sweated profusely. The lowest blood sugar noted was 0.04 per cent.—R. G. H.

The selective vasoconstrictor action of adrenaline. Clark, G. A., J. Physiol. 69: 171. 1930.

When enough adrenaline is administered to cause a rise in blood pressure there is a persistent cutaneous vaso-constriction accompanied by an increased blood volume in skeletal muscle and in the portal area. The latter effect is partly independent of visceral reflexes since it occurs after vagus and splanchnic section. When a rise in pressure is prevented by a mercury compensator there is intestinal vaso-constriction less pronounced than in the skin. This indicates that reduced capacity of the nervous system, increased cardiac activity together with cutaneous vaso-constriction all play a part in the increased blood pressure after adrenaline.—C. I. R.

The mechanism of epinephrine action. VI. Changes in blood sugar, lactic acid and blood pressure during continuous intravenous injection of epinephrine. Cori, C. F., G. T. Cori and K. W. Buchwald, Am. J. Physiol. 93: 273. 1930.

Observations have been made as to the changes produced in blood sugar and lactic acid of normal rabbits during continuous intravenous injection of epinephrine at rates ranging from 0.00005 to 0.001 mgm. per kilo per minute. The minimal effective rate of injection of 0.00005 to 0.0001 mgm. per kilo per minute produces an increase not only in blood sugar but also in blood lactic acid. This rate of injection is 30 times smaller than the maximal rate of discharge of epinephrine from the adrenals as recorded by Cannon and Rapport and 8 times smaller than the rate of intravenous injection which causes a rise in blood pressure of unanesthetized rabbits. In view of these facts the increase in blood lactic acid after epinephrine injections is regarded as physiologically significant. As soon as the injection is discontinued, both blood sugar and lactic acid begin to fall, showing that epinephrine is destroyed rapidly and that the after effect is of short duration. These points are also illustrated in experiments in which 0.03 mgm. of epinephrine per kilo was injected at once into the blood stream. After such an injection the peak value of blood sugar and lactic acid is reached in 15 minutes or sooner and there is a return to normal in 1 hour. This is in contrast to the sustained and much larger increase in blood sugar and lactic acid to be observed when the same amount of epinephrine is injected in the course of 1 hour. The similarity between the sugar and lactic acid curves in blood observed after subcutaneous and after continuous intravenous injection of epinephrine is emphasized. The smallest rate of injection of epinephrine which causes a perceptible rise in the blood pressure of unanesthetized rabbits is close to 0.00008 mgm. per kilo per minute.—Authors' Summary.

Variability of the abdominal paraganglia in childhood (Variabilitäten der abdominalen Paraganglien im Kindesalter). Iwanow, G., Ztschr. f. Anat. u. Entwicklsg. 91: 404. 1929.

Largely topographical. Periods of increase and decrease are plotted to 13 years of age. A rapid increase in number and size occurs during the first year and a half, followed by a slow decline, reaching a minimum at about 5 years of age. The blood and lymph supply is briefly discussed.—A. T. R.

The effects of x-rays on the adrenal gland. Rogers, F. T. and C. L. Martin, *Am. J. Physiol.* 93: 219. 1930.

The direct application of x-rays of an intensity estimated as three and one-half human erythema doses to the one exposed adrenal gland of dogs, after the excision of the other gland, produced no subsequent changes in the gland except a slight fibrosis. No functional disturbances appeared in these animals during a period of observation of from three to twelve months after the irradiation. The application of six to eight doses to the adrenal gland produced no observable functional disorders in dogs kept three months after irradiation, although fibrous proliferation in the gland can be demonstrated microscopically. Adrenal deficiency symptoms can be induced in dogs by the surgical excision of one gland and giving excessive x-ray doses to the remaining gland, but the lapse of several months may be required for their appearance. These effects are as follows: the gradual onset of a progressive muscular weakness, depression of metabolism, and terminal lowering of the blood chlorides and death. Heavy dosage of x-rays to the exposed adrenal gland induces degenerative changes, first in the medulla of the gland, and then of the zona reticularis and zona glomerulosa and an extensive proliferation of fibrous tissue throughout the gland.—Authors' Summary.

The effect of restricted diet and suprarenalectomy on experimental tuberculosis in the white rat. Steinbach, M. M., *Proc. Soc. Exper. Biol. & Med.* 27: 142. 1929.

Bilateral suprarenalectomy in the rat appears to lower the resistance so that subsequent inoculation with bovine tubercle bacillus results in definite tissue reaction, with tubercle formation and caseation, resembling human tuberculosis. This does not occur in normal rats or in rats on restricted diet. Suprarenalectomy and, to a less extent, deficient diet increase the susceptibility of rats to the avian tubercle bacillus.—M. O. L.

Sulphate retention in dogs following bilateral adrenal extirpation. Swingle, W. W. and W. F. Wenner. *Physiol. Zööl.* 1: 37. 1928. *Abst., Biol. Absts.* 3: 1206. 1929.

Acid-base equilibrium tests in adrenalectomized cats show that animals presenting symptoms of adrenal insufficiency are suffering from an uncompensated non-volatile acidosis. The acidosis was attributed to phosphoric and undetermined organic acids (the organic acid including the sulphate ion because of inability to test for it separately). The present experiments show that the sulphate ion plays an important role in the acid intoxication. The chief results are as follows: Retention of inorganic sulphate occurs following the onset of serious symptoms of adrenal insufficiency. Values as high as 14 mgm. are not uncommon. Unilaterally operated dogs and bilaterally operated animals showing no symptoms have normal amounts of inorganic sulphate in the blood, i. e., values ranging from 0.9 mgm. to 2.5 mgm. per 100 cc. The increase in inorganic sulphate parallels the increase in inorganic P and N. Sulphate and phosphate retention are sufficient to account for the degree of acidosis observed in adrenalectomized dogs. Organic acid is not so important a factor in inducing the fall in bicarbonate as the phosphate and sulphate. With the exception of those types of nephritis characterized by N retention and acidosis, adrenal insufficiency is the only other condition where sulphate retention occurs. This is further evidence that the suprarenal cortex is necessary for the maintenance of normal kidney function.

Problems of age (*Problémy Stáří*). Eiselt, R., *Bratisl. lékař. listy*, 9: 158. 1929.

The work is divided into three principal parts: biology, clinic and pathology of age. In the first part, the author discusses the physical chemistry of colloidal matter, the theory of protoplasmic hysteresis (Ruzicka) and the opinions of Lumière. In the clinical part, the changes brought about by disturbances of internal secretions are discussed, first of all the genital glands, thyroid, adrenals, and hypophysis, which determine a new old age terrain, and on account of which in advanced years new symptoms of disease and even modifications of disease make their appearance. In advanced years hypothyroidism predominates, yet a decided myoedema is relatively seldom observed. The insufficiency of the parathyroids seldom leads to pronounced

tetany; as a rule, only an augmentation of the mechanical nervous irritability is observed. The influence of the parathyroid is often shown in the metabolism of calcium which often amounts to osteoporosis. The hypophyseal changes show themselves mostly in acromegaly which often occurs in older women. In senility, the hypofunction of the genital glands is of first importance, i.e. as hypofunction of the interstitial gland in males and of the corpus luteum in females. Whether the operations according to Steinach and Voronoff really have in whole sense of the word the effect of rejuvenation, whether they have the sense of a stimulant therapy, or whether there exists really a regeneration of the function of the internal secretion of the genital glands, has as yet not been indisputably proved. In the third part, which treats the pathology of age, diseases to which old age is most subject and which influence the general constitution of individuals, are discussed. To this category belong, first of all, atheroxerosis and atherosclerosis which are the cause of 52% of deaths. Disturbances of the vegetative nervous system and vasomotor cramps lead to dyspragia and Raynaud's disease, atheroma of the vessels leads to embolism and thrombosis, which in turn lead to senile gangrene. The weakness of the heart is the cause of gradual diminution of blood-pressure which gives rise to disturbances in the nourishment of various organs; viz., that of the central nervous system. Tuberculosis of the lungs often appears in old age and is the cause of 20% of deaths.—Author's Abst. Abbreviated.

**Sexual influence of non-sexual endocrine glands.** Virility action of the supra-renal and hypophyseal substances (*L'influence sexuelle des glandes endocrines non-génitales*). L'action virilisante de la substance cortico-surrénale et de l'hypophyse). Marañón, G. *Rev. franç. d'endocrinol.* 8: 1. 1930.

A review of the literature citing evidence that both glands are significant factors.—R. G. H.

**Physiology of the corpus luteum. V. The preparation and some chemical properties of progestin, a hormone of the corpus luteum which produces progestational proliferation.** Allen, W. M., *Am. J. Physiol.* 92: 174. 1930.

An improved procedure for the preparation of a hormone of the corpus luteum which produces progestational proliferation is described, and evidence is presented to show that it is destroyed by alkalis, thus differentiating it chemically from oestrin. The purified product is not destroyed by mild acid hydrolysis nor is it associated with cholesterol color-reactions. It is relatively stable to heat and mild oxidation. Data are given regarding the yields of active substance. The oily preparations deteriorate rapidly but they may be kept in ethyl alcohol for long periods of time without loss. The name "progestin" is proposed for this specific hormone of the corpus luteum.

—Author's Summary.

**Physiology of corpus luteum VII. Maintenance of pregnancy in rabbit after very early castration, by corpus luteum extracts.** Allen, W. M. and G. W. Corner. *Proc. Soc. Exper. Biol. & Med.* 27: 403. 1930.

Female rabbits were doubly ovariectomized 18 hours after mating. Corpus luteum extracts, prepared by the authors, were administered daily subcutaneously. In 4 animals pregnancy was maintained until full term and spontaneous delivery. In 2 animals fully developed dead fetuses were found on the 34th and 36th days.—M. O. L.

**Hormone content of human ovarian tissues.** Allen, E., J. P. Pratt, Q. U. Newell and L. J. Bland, *Am. J. Physiol.* 92: 127. 1930.

Analyses of hormone content of isolated tissues of the human ovary have been made by injections of fresh follicular fluid and by implantation of fresh corpora lutea, of follicle walls and of cortical stroma free from macroscopic follicles. The use of graded amounts of ovarian tissues has made possible roughly quantitative analyses. The test used as a criterion of hormone activity was the full oestrous reaction of the ovariectomized rat as reflected in the cell content of the vagina. Therefore the hormone sought was that responsible for the genital growth reactions of the periods of oestrus in lower mammals and of the intermenstruum in primates. Three of the recent corpora lutea tested

corresponded to unfertilized ova recovered from the uterine tubes. The stages of development of these and other corpora has been checked by histological studies. High yields of this hormone have been obtained from recent corpora removed from the 13th to 17th days of the menstrual cycle. There is a considerable decrease in amount by the 20th to 22nd day. Corpora of the first third of gestation contain considerable amounts. Two full term corpora gave negative tests. This last result indicates definitely that toward the end of gestation the corpus luteum of woman does not share responsibility for the large amounts of this hormone in the placenta, blood and urine. Liquor folliculi and pieces of follicle wall (mostly granulosa cells) contained considerable amounts of this hormone. In most cases the specimens tested were diagnosed as to normality or atresia by study (in section) of the follicle wall or the contained ova. In two cases of long continued bleeding large yields of hormone were obtained from cystic follicles. In one case of amenorrhea, large amounts of fluid from cystic follicles returned negative tests. Cortical stroma without macroscopic follicles, taken from ovaries containing follicles or corpora in which hormone was demonstrated, gave negative tests. These results added to earlier data demonstrate that, as far as the secretion of this hormone is concerned, the human corpus luteum merely continues an activity which is primarily follicular. This hormone content of the human corpus is highest just after ovulation in the early stages of transition from follicle to corpus luteum and decreases before the onset of the next menses. Normal stroma tissue of the ovarian cortex shares little in this function. Removal of parts of ovaries most active in secretion of this hormone, either large follicles or recent corpora lutea,—when done during the intermenstruum, usually results in the appearance of menstruation within the next 48 hours. These observations substantiate earlier conclusions from experimental work in monkeys that menstruation is degenerative in significance and primarily due to decreased action of this ovarian hormone after it has induced a certain amount of growth in the uterus.—Authors' Summary.

**Folliculin and periodicity of sexual cycle (Ciclo sexual periódico y folliculina).** del Castillo, E. B., and C. J. Calatroni, *Rev. Soc. argent. biol.* 6: 108. 1930.

Daily injections of 0.1-2 units of folliculin were made in rats during several months. A latent period, summation of effect, after discharge and tendency to periodicity more marked with time, were observed. In castrates in spite of continued injections periodic oestrus was observed. Ovary and corpus luteum are therefore not indispensable for periodicity of cycle. Uterus and vagina have a periodic activity, autonomous or governed by an unknown factor, which is made manifest by the presence of folliculin.—J. T. Lewis.

**Clinical experiments with oestrin.** Dodds, E. C. and J. D. Robertson, *Lancet*, 218: 1390. 1930.

The results of treating 86 cases with an accurately standardized preparation of oestrin are described. The conditions investigated were amenorrhea, menopause symptoms, and attempts to produce premature labor. Out of the 86 cases treated only about 30 showed objective improvement, onset of menstruation, abatement of vasomotor and nervous symptoms, or induced labor. The authors discount general improvement as a psychological effect, but consider further investigation with larger doses desirable.—M. A. Reid.

**Development of the gonads in man (Über die Entwicklung der Keimdrüsen des Menschen).** Fischel, A., *Ztschr. f. Anat. u. Entwicklungsg.* 92: 34. 1930.

Interstitial cells are first demonstrable in the 42 mm. stage and are of mesenchymal origin.—A. T. R.

**Intersexuality or hermaphroditism in mammals (Intersexualität oder Hermaphroditismus bei Säugetieren).** Krediet, G., *Ztschr. f. Anat. u. Entwicklungsg.* 91: 251. 1929.

The author discusses the histology of the gonads in correlation with the sex characteristics of hermaphrodite mammals, particularly in the pig, goat and man.—A. T. R.

The relation of basal metabolism to gestation. Litzenberg, J. C. and J. B. Carey, *Am. J. Obst. & Gynec.* 17: 550. 1929.

This study is concerned with women having a metabolic rate slightly below normal, and showing no other signs of myxedema. The material was derived from 2,500 consecutive determinations of the basal metabolic rate in all types of patients, of whom 758 had a rate of minus ten or lower. In 91 cases of sterility, 52 women had a metabolic rate below normal; 36% had abnormal menses. These 52 women were treated with thyroid extract upon the supposition that the low rate was due to thyroid influence. Following this treatment, 30% of them became pregnant, two aborted (treatment was discontinued after conception), while 15 of the same group had aborted one or more times before treatment. Of a group of 137 women with lowered metabolism, 45% were sterile. There is a definite relation between metabolism and reproductive function. Lowered metabolism interferes with the function of reproduction in a large percentage of cases.—J. C. Litzenberg.

Action of predigested corpus luteum on excised vas deferens. Macht, D. I., A. E. Stickels and H. P. Leach, *Proc. Soc. Exper. Biol. & Med.* 27: 152. 1930.

The most vigorous digestion of corpus luteum substance with pepsin or with pancreatin and bile did not decrease the potency of extracts of these corpora to cause contraction of the vas deferens.—M. O. L.

Concerning the different hormones and tissue respirations. III. Concerning castration and tissue respiration (*Ueber die verschiedenen Hormone und die Gewebsatmung*). III. Ueber die Kastration und die Gewebsatmung). Maeda, M., *Folia Endocrinol. Japon.* 5: 101. 1930.

The author studied the influence of castration upon the tissue respiration of adult rabbits by means of Barcroft's manometer according to Warburg's method 2 or 3 months after castration. In male castrated animals the oxygen consumption is increased in the thyroid and decreased in the adrenals and pancreas, while the oxygen consumption of the spleen shows no change. The oxygen consumption of castrated female animals is increased in the thyroid and to a lesser degree in the adrenals. In the pancreas and spleen the respiration is unchanged. In the liver of castrated animals of both sexes the oxygen consumption remains practically unchanged, while the CO<sub>2</sub> production increases.—J. Gagnon.

The chemistry of oestrin. III. An improved method of preparation and the isolation of active crystalline material. Marrian, G. F., *Biochem. J.* 24: 435. 1930.

By acidification and ether-extraction of urine from pregnant women, yields of oestrin varying from 8000 to 40,000 mouse units per liter can be obtained. Methods described by which these extracts can be greatly purified with a loss of only 40% of the activity throughout the process. This loss occurs entirely in the initial stage of saponification. The mouse unit of these purified preparations is of the order of 0.0006 mgm. From such purified preparations an active crystalline substance has been isolated. The mouse unit of this substance is about 0.00011 mgm. The possible identity of this substance with the active substances recently isolated by Butenandt and by Laqueur, Dingemans and Kober is discussed. There is no proof at present that this substance is actually the pure hormone.—Author's Summary.

The relative amounts of oestrin required to produce the various phenomena of oestrus. Marrian, G. F. and A. S. Parkes, *J. Physiol.* 39: 272. 1930.

The effective dose for the mouse is 200 units. On this basis 400,000 units would be required for the average woman which is much larger than is ordinarily given clinically.—C. I. R.

Physiologic effects of non-living testis grafts. Moore, C. R., *J. A. M. A.* 94: 1913. 1930.

The author reports on 3 experiments and concludes that the spermatozoon motility test provides a means of revealing the presence of testis hormone in guinea pigs for periods as short as 10 days; yet by means of this test it has

been impossible to detect any hormone liberated from two autoplasmic, whole testis grafts placed in subcutaneous pockets. In the rat a cytologic study of the prostate gland and seminal vesicles affords dependable methods of detecting the absence of hormone for periods of from 3 to 5 days. Here, also, two autoplasmic, whole testis grafts in subcutaneous pockets fail to delay the onset of castration changes for as short a period as 2 days. The autolysis of nonviable testicular grafts does not liberate hormone in amounts that can be detected by any means at present known. Furthermore, the testis hormone is not stored within the body but is excreted by the kidneys. A continuous supply is necessary to maintain the secondary sex characters in a normal condition. There is no known acceptable evidence that nonviable testis grafts, i. e., grafts that fail to become incorporated within the body and actively secrete, exert any immediate or remote beneficial effect on the host organism.

**Cholesterol in blood and bile during and after delivery and cholesterol in foetal blood** (*La colessterina sanguinea y biliar durante el embarazo y puerperio. Colesterinemia fetal*). Palacios Costa, N. and M. V. Falsia, *Rev. Soc. argent. de biol.* 6: 99. 1930.

Blood cholesterol was found to be increased in 30 pregnant women (0.262% average); during labor a further increase occurred; on the seventh day after delivery it had fallen to 0.172%. Blood serum from the umbilical cord had an average of 0.108%, no relation being found with the amount in the mother's blood. Bile cholesterol was 0.121%. When blood cholesterol was above 0.3% there was a corresponding increase in the bile cholesterol.

—J. T. Lewis.

**Causes of Parturition** (*Investigaciones sobre la causa del parto*). Perez, M. L., *Rev. Soc. argent. biol.* 6: 75. 1930.

Transfusion of citrated blood of women in labour to women in the last stage of pregnancy produces symptoms of labour and delivery in 60%.

—J. T. Lewis.

**Adsorption of the ovarian hormone from urine.** Wiles, H. O., *Proc. Soc. Exper. Biol. & Med.* 27: 125. 1929.

Ovarian hormone may be adsorbed quantitatively from urine by calcium phosphate.—M. O. L.

**Source of the pigmentary hormone of the amphibian hypophysis.** Allen, B. M., *Proc. Soc. Exper. Biol. & Med.* 27: 504. 1930.

Unmixed pars intermedia of frog hypophysis transplanted into normal or hypophysectomized tadpoles becomes functional and causes maximal expansion of the superficial melanophores and deposition of pigment in the epidermal cells. Transplants of pure pars nervosa tissue do not cause pigmentary effects, while pars anterior tissue causes only a slight transitory effect.

—M. O. L.

**Potent, sterile and low-protein extracts of the growth hormone from the anterior hypophysis.** Evans, H. M., R. E. Cornish and Miriam E. Simpson, *Proc. Soc. Exper. Biol. & Med.* 27: 101. 1929.

Procedures are given for the preparation of a sterile, low-protein extract of anterior lobe which caused marked increases in body weight of adult female rats when injected daily intraperitoneally. The anterior lobes had been stored for 18-24 months with solid CO<sub>2</sub>. During the preparation of the extract, the temperature was never above 10°C. About 15 liters of extract was obtained from 2,000 grams of anterior lobes. The total solid content of the extract was about 1.1%.—M. O. L.

**Anterior lobe of the pig and the monkey ovary.** Hartman, C. G., *Proc. Soc. Exper. Biol. & Med.* 27: 338. 1930.

An adult female rhesus was found to have a small uterus and minimal sized ovaries. Implantations of two anterior lobes from adult castrated pigs were given for 4 days. Nine days later at a laparotomy the uterus was found to be much enlarged and the ovaries were of relatively enormous size, with the entire surface studded with graafian follicles.—M. O. L.

Hypophysectomy and pancreatic diabetes in toads (*Hipofisectomía y diabetes pancreática en el sapo*). Houssay, B. A. and A. Biassotti, *Rev. Soc. argent. biol.* 6: 8. 1930.

Further studies in 1200 *Bufo arenarum* showed that pancreatectomy is followed by diabetes with hyperglycemia and glycosuria. Simultaneous removal of the pituitary and the pancreas is not followed by glycosuria, and hyperglycemia is not constant and never very marked. Extirpation of the pancreas and the glandular lobe of the pituitary is followed by the same effects. If pancreatectomy and hypophysectomy are followed by daily implantations of anterior lobe, intense diabetes with hyperglycemia and glycosuria ensues. Lesion of the tuber cinereum prevents, in nearly all cases, pancreatic diabetes. If implantations of glandular lobe are made it appears as usual. The neuro-intermediate lobe has a similar but less marked effect. No other tissue of the toad is active in this respect. Therefore the glandular (anterior) lobe of the pituitary is an important factor in the production of pancreatic diabetes in the toad.—J. T. Lewis.

Sexual functions, pituitary and diencephalon in toads (*Funcion sexual, hipófisis e hipotalamo en el sapo*). Houssay, B. A. and L. Giusti, *Rev. Soc. argent. de biol.* 6: 146. 1930.

Implantation of anterior lobe produces an increase in the volume and activity of testicles and subsequently increased sexual flexion reflex (not observed in castrates). Testicular implantation does not produce such effects. Injection of large doses of testicular extracts produces flexion reflex in castrates. Cauterization of infundibulum produces intense flexion reflex even in castrates and after hypophysectomy. This last operation also produces ovulation and expulsion of ova which is not observed after extirpation of the pituitary or of only the glandular lobe. Hypophysectomy or extirpation of glandular lobe when complete did not produce ovulation (rectifying previous communications). Pituitary of *Bufo arenarum*, *B. d'Orbigny* and *L. ocellatus* are active for these species. Alkaline extracts of mammalian pituitary, exceptionally produce incomplete ovulation in toads.—J. T. Lewis.

Tumors of the hypophysis, especially of the hypophyseal region and the mid-brain (*Geschwülste der Hypophyse, bzw. der Hypophysergegend und die Zwischenhirns*). Illig, W., *Virchow's Arch. f. path. Anat.* 270: 549. 1928.

Four cases are reported in which tumours were found in or about the pituitary. In a male aged 76 who died suddenly an eosinophilic adenoma was found in the pars anterior. The pituitary weighed 2.9 gms. (normal 0.6 gms.). There was no history of pituitary symptoms. A male aged 14 complaining of paralysis of the right abducens nerve and of right exophthalmos showed pronounced displacement of the pituitary by a sarcoma invading the skull. The third case, a male aged 46 with a history of right sided loss of hair for 8 years showed improvement on x-ray treatment but dystrophia adiposogenitalis gradually developed in the following 6 years. Pathological investigation disclosed a chief cell adenoma of the pituitary and regression changes about the ventricles. A female aged 45 who complained of headache, emaciation and disturbed speech and vision, on post mortem examination disclosed a chief cell adenoma of the pituitary, a cortical adenoma of the adrenal, acute cystitis and degeneration in the ganglion cells about the ventricles (hypophyseal cachexia). The writer concludes that the symptoms of pituitary disorder are still obscure and that the pathology of dystrophia adiposogenitalis and of hypophyseal cachexia remains in doubt. Clinical and pathological details of the 4 cases are supplied and fully discussed.—W. Susman.

Influence of extracts of hypophysis on the body weight, weight of fat, of sexual organs and of endocrine organs of rats. Korenchevsky, V., *Biochem. J.* 24: 383. 1930.

An alkaline glycerol extract of fresh anterior lobe when injected into rats caused no marked increase in body growth, but did decrease intra-abdominal fat, and caused a decrease in the weight of the penis, prostate, seminal vesicles, testes and thyroids.—M. O. L.



**Influence of extracts of hypophysis on nitrogen metabolism.** Korenchevsky, V., and M. H. Dennison, *Biochem. J.* 23: 868. 1929.

The oral administration of dried anterior or posterior lobe substance had no significant effect on urine flow or nitrogen metabolism in rats and rabbits. The subcutaneous injection of glycerol-water extracts of fresh anterior lobe produced on the day of the injection a decreased urinary flow and a decrease of 27% in the nitrogen metabolism. On the following day the nitrogen excretion remained depressed in rabbits, but increased above the normal in rats; urine volume was considerably increased.—M. O. L.

**Oral administration of anterior pituitary tablets and our laboratory preparations on compensatory hypertrophy of thyroid gland.** Loeb, L. and W. J. Siebert, *Proc. Soc. Exper. Biol. & Med.* 27: 495. 1930.

Compensatory hypertrophy of the remnant of thyroid gland in guinea pigs, after the removal of one lobe and  $\frac{1}{2}$  to  $\frac{3}{4}$  of the other, was much diminished or entirely prevented by feeding daily a tablet of Armour's anterior pituitary substance. The feeding of anterior lobe substance prepared in Loeb's laboratory did not prevent the normal compensatory hypertrophy or diminished it only slightly. Fifty-four guinea pigs were used.—M. O. L.

**The hypophysis in old age (L'hypophyse chez le vieillard).** Lucien, M., *Rev. franç. d'endocrinol.* 6: 441. 1929. *Abst., Arch. Neurol. & Psychiat.* 24: 170. 1930.

After making a series of studies of the hypophysis in the aged, Lucien draws certain conclusions. He does not believe that one should speak of senile atrophy of the hypophysis, since in the anatomic study of the gland there is no evidence that there is reduction in its size or weight during the process of ageing. On the other hand, it is of note that the largest and heaviest pituitary glands have been found in old people. Microscopic study reveals areas which might be described as sclerosis, areas which are localized especially in certain parts of the gland, for example, at the hilus and near vascular pedicles, do not take on a different staining reaction and therefore should not be the cause of atrophy of glandular elements. He considers that the glandular parenchyma does not seem definitely reduced. The author expresses the opinion that histologic changes observed are evidence of a special functional state, which is peculiar to the hypophysis of old age. He calls attention to the fact that changes in the gland noted in old age have certain characteristics in common with changes occurring in some chronic nervous disturbances, such as chronic encephalitis and dementia paralytica. In the latter, there is evidence, besides a sclerosis, of a tendency toward enlargement of the acidophil cells. He considers, therefore, that the changes seen in the hypophysis of old age seem to be partly the result of an inflammatory process. This theory presupposes a new functional state of the hypophysis in the decline of life which is characterized by the accumulation of colloid substance in the lobes of the gland where pseudo-acinous forms are numerous; by the development of colloid vesicles around the hilus, and by the presence of a considerable amount of colloid in the pars nervosa. Thus, it would seem that there is in the hypophysis of the aged a true retention of colloid substance in the different parts of the gland. Secretory phenomena are in general slowed up, the acidophil elements being the only parts of the gland which preserve evidence of true glandular activity. The invasion of the posterior lobe by the basophilic cells of the pars intermedia is a contradiction of the hypothesis of slowing up of secretory phenomena. The migration of the acidophils into the pars nervosa would seem to indicate an active multiplication of these elements. The author interprets it in a different fashion. In normal functions of the hypophysis, cells of the pars intermedia emigrate to the pars nervosa where they slowly disappear by granular necrobiosis. The enigmatic bodies of Soyer represent these elements in the process of disintegration, and a collection of colloid in the neuro-hypophysis should be considered the result of this cellular piling up. This theory has been verified from experimental observations on the hypophysis of the cat. In the aged, emigrating cells, of the type found in the pars intermedia, progress little by little to the pars nervosa where their degeneration later shows itself. There is a slowing up of the cellulolytic processes and an accumulation of

basophilic cells in the neuro-hypophysis. Changes shown in the hypophysis of the aged may be an expression of a general slowing up of secretory function and a marked reduction of excretory function, of which the collected colloid is the most characteristic manifestation.

Effect of oestrin on gonad stimulating power of the hypophysis. Meyer, R. K., S. L. Leonard, F. L. Hisaw and S. J. Martin, *Proc. Soc. Exper. Biol. & Med.* 27: 702. 1930.

Thirty-four immature female rats were given 2 r. u. per day of oestrous hormone for 30 to 70 days. Their pituitaries were then implanted into female rats 20 to 30 days old. The vaginas of these rats opened 9 to 25 days after the implantations, as compared with 4 to 5 days in similar rats receiving pituitary implants from controls which had not been injected with oestrous hormone. In further experiments male and female adult rats were castrated, and some of each sex were injected daily with 4 r. u. of oestrous hormone for 31 days. Their pituitaries were then implanted into immature female rats. The vaginas of the control and experimental recipients opened at about the same time but the ovaries of the experimental recipients weighed considerably less than the ovaries of the control recipients. The difference averaged 28% less for the male donors and 35% less for the female donors. The authors believe that the oestrous hormone inhibits the normal development of the ovary and decreases the gonad stimulating power of the hypophysis, and that the hypophysis of the female is more susceptible than that of the male.—M. O. L.

The relation of diabetes insipidus to the posterior pituitary and the tuber cinereum (Über die Beziehungen des Diabetes Insipidus zum Hypophysenhinterlappen und zum Tuber cinereum). Sato, T., *Arch. f. exper. Path. u. Pharmakol.* 131: 45. 1928.

Hypophysectomy of dogs was followed by a temporary or lasting polyurea in some but not in all cases. During the first week following successful hypophysectomy the amount of the oxytocic substance of the cerebrospinal fluid was below normal. After that period it became equal to that of normal cerebrospinal fluid. Extracts of the tuber cinereum of normal dogs contain a relatively small amount of oxytocic and of antidiuretic substance. Eight days after hypophysectomy they have a relatively high content of both. The theory is advanced that diabetes insipidus is produced by a deficiency in the antidiuretic substance of the posterior lobe extract and that whether or not it appears after hypophysectomy depends on whether or not the tuber cinereum is also destroyed.—Helen Bourquin.

Effect of various anterior pituitary preparations on basal metabolism in guinea pigs. Siebert, W. J. and R. S. Smith, *Proc. Soc. Exper. Biol. & Med.* 27: 622. 1930.

Daily subcutaneous injections of either acid or alkaline extracts of beef anterior lobe caused in guinea pigs a marked and rapid rise in basal metabolism, which reached a maximum of approximately +60% within the first 10 days. Then the basal metabolism gradually returned to a level approximately 15% higher than the average found in normal guinea pigs. Feeding daily one 5 grain Armour anterior pituitary tablet to a guinea pig caused a gradual steady rise in basal metabolism which reached a maximum of approximately +60% in about 30 days. Feeding daily 5 grain pills of dried anterior pituitary substance prepared in Loeb's laboratory caused a slight gradual rise in basal metabolism which reached its maximum of approximately +25% in about 20 days, after which there was a gradual return to almost the normal level. Daily subcutaneous inoculations of fresh guinea pig anterior pituitary gland tissue caused a very slight gradual rise in basal metabolism which reached a maximum of approximately +15% in about 5 days, after which there was a decline.—M. O. L.

Biedl's disease (Biedlsche Krankheit). Sereissky, M., *Med. Klin.* 25: 1620. 1929.

The author states that as cases of Biedl's disease occur isolated and the number of cases cited in the literature up to the time of the present case is scarcely above 30, it is imperative that such cases be reported. His case (fe-

male, single, 27 years) presents the following syndrome: adiposity, pigment retinitis, polydactylism, deformation of the cranium with a high grade of mental retardation and imbecility bordering on idiocy. Symptoms of hypogenitalism are absent and in this respect the case is similar to that reported by Curschmann and Deusch. Onset of the disease was in early childhood and was marked by its slight progress. The change in the sella turcica distinguishes it from those of Biedl. Ratner considers this change a stigma of "diencephalic insufficiency." The fact that this patient was born in asphyxia and forceps were used merits consideration. There are two noteworthy facts which deserve especial attention: (1) Speech was slow in developing—patient first began to speak when 4 years old—and diction was only slightly altered; (2) Heredity—the presence of a pigment retinitis as a recessive indication and the polydactylism as a dominant sign in the clinical picture point to the rôle of hereditary factors. There is marked resemblance to the amaurotic idiocy and especially to the mutation form. The reference of authorities to hypophyseal-intermediary insufficiency in amaurotic idiocy and the hereditary nature of this disease justifies the attempt to place the Biedl syndrome in the heredo-degeneration group to which amaurotic idiocy belongs.—H. G. Beck.

What are the effects of roentgen ray irradiation of the pituitary gland in the treatment of the disorders of the menopause? (Was leistet die Roentgenbestrahlung der Hypophyse bei Behandlung klimakterischer Beschwerden?) Steinhard, B., Klin. Wchnschr. 8: 1717. 1929. Abst., Arch. Physical Therapy, 11: 250. 1930.

The author terms the results of x-raying the pituitary gland in climacteric disorders excellent. The favorable effect in climacteric disorders after roentgen castration is especially to be stressed. Technique: both temporal fields were given in one exposure  $\frac{1}{2}$  of the skin unit dose each. Also in favorably reacting cases the first irradiation only achieves an improvement of mostly about from 4 to 8 weeks' duration; after a second series the success mostly lasts for from about 4 to 5 months; a permanent success is in the majority of cases only to be obtained after the third or fourth series. Treatment should therefore not be discontinued prematurely. Vasomotor symptoms as hot flashes, outbreaks of sweat, headache, vertigoes are for the most part favorably influenced, which statement, however, cannot be advanced in regard to arthralgias of the menopause. The author points out, finally, that ovarian hormone therapy and bleeding, too, failed in those few cases, in which irradiation had also failed.

Simmond's disease (Über die Simmondsche Krankheit). Subotitza, K. H., Klin. Wchnschr. 7: 944. 1928.

Simmond's disease is a chronic disease of the anterior pituitary and its early symptoms are loss of appetite and the falling out of the teeth. Achlorhydria follows and later the skin has an alabaster appearance. Anaemia, adynamia and cachexia are frequently present. Under präphyson administration (extract of anterior pituitary) rapid improvement follows. A female of 53 suffering from gastric symptoms, glaucoma, general weakness, emaciation, loss of hair and teeth, mental dullness, eosinophilia, subnormal blood sugar and a tolerance for insulin was first diagnosed as a case of myxoedema. New growth, pernicious anaemia and intestinal parasites were excluded. After thyroid treatment the response was slight and further investigation resulted in the diagnosis of Simmond's disease. Under präphyson the improvement was very pronounced. The action of präphyson is discussed as to its effect on the individual symptoms and as to the route by which it acts. So also are the symptomatology, differential diagnoses, and treatment of the disease considered.—W. Susman.

Effect of certain liver extracts on the blood sugar of diabetic patients. Blotner, H. and W. P. Murphy, J. A. M. A. 94: 1811. 1930.

A study of the effect of the oral administration of certain liver extracts on the blood sugar of 23 diabetic patients indicates that they had a beneficial effect on the blood sugar of these patients. These extracts were prepared by making an aqueous extraction of calf's liver at from 35 to 40 C. at a pH of from 4.6 to 5.2 and then evaporating and precipitating this aqueous extract

at certain temperatures to varying degrees of dryness according to the method given in this paper. The average decrease in the blood sugar 8 hours after the control test meal in 18 out of 19 diabetic patients was 32.2 mgm.; the average decrease 8 hours following the test meal with the addition of the liver extract was 79.8 mgm. in these cases; while the average decrease in the 12 diabetic patients that were given the test meal and 10 units of insulin subcutaneously was 67.9 mgm. for the same period of time. Four patients with diabetes taking an aqueous extract have been observed with repeated fasting blood sugar determinations for 68 days, 29 days, 31 days and 5 months, respectively. In the first case the blood sugar remained at a lower level when the liver extract was taken, and then increased when it was omitted. In the second case the blood sugar was also at a lower level during liver extract therapy than previously, and when 7 units of insulin was injected subcutaneously twice a day the blood sugar level was slightly lower than during the period of liver extract therapy. In the third case the blood sugar level during liver extract therapy was at a slightly higher level than during the period when 13 units of insulin was taken. This may have been affected by the use of increased sedatives during this time. In the fourth case the blood sugar was stabilized by the liver extract, and the urinary sugar was decreased. These observations suggest that certain aqueous liver extracts contain a blood sugar reducing substance, active when taken by mouth, nontoxic and with an effect on the blood sugar concentration similar to that obtained with small doses of insulin, especially over a period of 8 hours.—Authors' Summary.

Secondary effects of insulin (*Nebenwirkungen von Insulin*). Bonem, P., München. med. Wchnschr. 70: 1585. 1929.

A report is made of insulin anaphylaxis in three patients with idiosyncrasies, manifesting skin and mucous membrane rash and gastro-intestinal symptoms. In one case the author thinks that four years previously when the patient received insulin, she became sensitized so that when it was resumed the anaphylaxis occurred. Changing the make of insulin made no difference. Reactions here described occurred after ingestion of eggs.

Diabetic ketosis and functional renal insufficiency. Coburn, A. F., Am. J. M. Sc. 180: 178. 1930.

The author divides his group of 122 instances of severe ketosis into 2 classes; 30 patients treated without insulin and 92 cases treated with insulin. Only two patients of the group treated without insulin recovered. In the cases treated with insulin diuresis was important if the coma was to disappear rapidly. The rapidity of the change from coma to health was directly proportional to the diuresis of acetone bodies. The intravenous infusion of hypertonic fluids containing glucose and alkali was the most efficient in causing excretion of acetone bodies. The author believes that excretion of acetone bodies is more important than their oxidation and also that development of anuria should be prevented.—E. L.

Relation of obesity and the tendency to the island organs (*Beziehung von Mast und Fettsucht zum Inselorgan*). Fajta, W., Wien. klin. Wchnschr. 43: 289. 1930.

Overinsulinization produces hypoglycemia, this in turn causes hunger, which is in turn followed by increased food intake and thus increase in weight. Increase in weight is not due altogether to the amount of food taken in, but to the amount which is metabolized and the oversurplus deposited as fat. Thus, it has been shown that patients on a constant diet, if given insulin, increase in weight up to a certain point at which they remain stationary. If the amount of insulin is increased, then the weight rises further and again becomes constant at this level. There is a limit to this, however, because when insulin is pushed above the limit, hypoglycemia occurs and with it the loss of weight. In insulin administration, even when the exogenous insulin is omitted often, the body weight keeps on increasing. This increase, heretofore, (in non-diabetics) could not have been brought about by the mere increase in diet, which speaks for the "training" of the islands to do more work. A review of the literature is given.—H. J. J.

**The problem of pulmonary tuberculosis in patients with diabetes.** Fitz, R., *Am. J. M. Sc.* 180: 192. 1930.

Of the 1529 diabetic patients treated, 35 had pulmonary tuberculosis. The prognosis of these patients is not good, as 19 of these cases terminated fatally in one year or less. The patients should receive the best diabetic care and an adequate diet.—E. L.

**A study of the relation of the blood sugar in plasma to that in the corpuscles in normal and diabetic individuals.** John, H. J., *J. Lab. & Clin. Med.* 15: 713. 1930.

The sugar content of the red blood corpuscles in the diabetic individual is strikingly lower than the sugar content of the surrounding plasma. As the amount of the sugar in the patient's blood increases, the increase occurs first in the plasma and does not appear until later in the red corpuscles. As the level of the plasma sugar falls, the corpuscular sugar as a rule keeps pace with it. Thus one rarely finds a higher sugar level in the corpuscles than in the plasma at the end of the glucose tolerance test, when the blood-sugar curve is descending. This relationship is not altered in severe cases of diabetes, that is, in cases in which the blood sugar is very high. In general, in the non-diabetic individual the corpuscles have a lower sugar content than the plasma, but this is not so marked as in the diabetic subject. In the normal subject, when the sugar in the plasma increases the corpuscular sugar rises more than it does in the case of a diabetic; but when the sugar curve is descending the corpuscles do not release their sugar so freely, and thus, as a general rule, one finds a higher level in the corpuscular sugar than in the plasma sugar at the end of the curve. A study of 1069 blood-sugar estimations shows that in nondiabetic individuals the ratio of the average increase of the sugar in the corpuscles, as compared with that in the plasma, to the average decrease was 17.12 to 12.20, while in diabetic individuals the corresponding ratio was 9.95 to 15.82. By suspending red corpuscles in 1000 mgm. per 100 cc. of glucose in a N/10 NaCl solution, the average increase of the corpuscular sugar after 2 hours was found to be 321% in corpuscles from nondiabetic individuals, and 185% in those from diabetic individuals. The washing of corpuscles in normal saline solution before their sugar content is estimated is contraindicated, as the sugar is washed out of the corpuscles and the estimations are therefore of no value. The present study would suggest that in diabetics the corpuscles have a lesser capacity to take in and to hold sugar than normally. Whether it is the decreased amount of insulin present or some other condition which is the dominant factor, future studies should disclose.—I. B.

**Pancreatic tumors and insulin secretion (Tumeurs pancréatiques et sécrétion insulinaire).** Lemaire, A., *Progrès. méd.* 44: 1205. 1929. *Abst., Rev. franç. d'endocrinol.* 8: 70. 1930.

This is a case of Langerhan's tumor of the pancreas with hepatic metastases and hypoglycaemia. This observation proves again that cancers developing at the expense of a glandular tissue are endowed with a secretion the effects of which are practically identical with those of the normal secretion of the original tissue. To the group of endocrine tumors already known, of which the remarkable observation of von Eiselsberg was the first, must now be added the Langerhansian adenomas and cancers. Hypoglycaemia by means of hyperinsulinism is the essential clinical interpretation of it.—Translated by J. Gagnon.

**Atrophy of subcutaneous fat associated with insulin injections.** Nichols, J. B., *Am. J. M. Sc.* 180: 90. 1930.

Prolonged hypodermic administration of insulin sometimes causes atrophy of the subcutaneous fatty tissues in the vicinity of the injections. In this paper a case of the kind is reported and 34 other cases in the literature are reviewed.—Author's Summary.

**Nondiabetic glycosurias.** Rowe, A. W. and Mary McManus, *Am. J. M. Sc.* 179: 761. 1930.

The etiologic background of a number of cases showing glycosuria but without demonstrable evidence of a diabetic condition has been studied. Certain non-endocrin states, including psychoses, lesions of the central nervous

system, primary anemia, lymphatic leukemia, malignant neoplasm, various types of hepatic dysfunction and syphilis, have shown a distinctive frequency of incidence of glycosuria. Further, certain of these conditions have appeared as complicating factors, in a group of patients with glycosuria whose primary complaint was not included in the list given above. Analysis of a similar series of disturbed endocrin functional states shows a similar incidence of glycosuria, even after those have been deleted which present the significant non-endocrin disorders as secondary complications. With but minor exception, all of the individuals show normal blood-sugar levels and the several group averages are entirely within conventional limits. The majority of the patients in the series show a depressed tolerance for galactose which is characteristic of the several conditions involved. Exception to the foregoing is noted in the case of thyroid failure, and far more strikingly in hypofunction of the pituitary, where increased galactose tolerance is occasionally associated with glycosuria. The same condition of glycosuria with normal blood sugar is noted in the physiologic state of pregnancy. It is concluded that the phenomenon of glycosuria is no more than one common end result of a wide variety of causes, many of which cannot be demonstrated to produce the effect through influence on or by the function of the pancreas. From this it is deduced that there are a number of factors concerned with the regulation of carbohydrate metabolism, of which the intrinsic function level of the islands of Langerhans, although most important, is but one.—Authors' Summary.

Studies on the circulation of the feet in diabetes mellitus with and without gangrene. Starr, I., *Am. J. M. Sc.* 180: 149. 1930.

As gangrene of the feet has been attributed to decreased blood supply, the blood flow through the feet was determined in a small number of cases. The histamine reaction was usually determined in four areas of the lower extremity. Both the wheal and the flare produced were observed in over one hundred cases. The histamine reaction shows that the majority of diabetics have a subnormal circulation in the feet, 32% being normal, 34% somewhat impaired and 34% markedly impaired. This reaction also aids in choosing the level for amputation in cases of gangrene.—E. L.

Serum calcium and phosphorus of guinea pigs after administration of single and repeated doses of parathormone. Bodansky, A., J. E. Blair and H. L. Jaffe, *Proc. Soc. Exper. Biol. & Med.* 27: 708. 1930.

In guinea pigs large doses (10 to 20 units per 100 gms.) of parathormone caused the serum calcium to rise to a maximum of about 16.0 mgm. about 24 hours after injection. Starvation did not intensify the effect in adult animals but did so in young pigs and also prolonged the effect. The serum phosphorus was modified in the same way, in general, although starvation of the adults intensified the effects somewhat. In doses as large as 30 units per 100 gms. given daily for several days, the serum calcium rose to 20 mgm. and serum phosphorus also rose to a high value. Doses less than 5 units per 100 gms. per day for 10 and 16 days had no apparent effects on serum calcium or phosphorus, but histological examination showed bone resorption, indicating mobilization and excretion of bone calcium in the absence of hypercalcemia.

—M. O. L.

Blood phosphorus and serum calcium in parathyroid deficiency. Esau, J. N. and O. O. Stoland, *Am. J. Physiol.* 92: 1. 1930.

The average of 261 determinations on 71 normal dogs showed the following concentrations: calcium 10.84 (mgm. per 100 cc. serum), inorganic P. 4.44, total acid soluble P 26.65 (in mgm. per 100 cc. of whole blood), inorganic P/Ca ratio 0.41, and total acid soluble P/Ca ratio 2.42. Although the phosphorus compounds, particularly of the skeletal muscles, may play a leading rôle in the symptomatology and death of parathyroid deficient dogs, the inorganic and total acid soluble phosphorus changes of the whole blood are not primarily etiological. In thyroparathyroidectomized dogs the inorganic P always increases, but the total acid soluble P tends to increase with the severity of the symptoms manifested. However, if the symptoms of parathyroid deficiency are mild and delayed in onset for 3 or more days there is usually a fall to below the normal. A low blood inorganic P and particularly a low total acid soluble P is highly favorable to recovery from parathyroid deficiency. The beneficial effects of magnesium lactate and morphine sulphate

despite a secondary progressive rise in inorganic P and total acid soluble P are attributed to their depressant action on the respiratory center and other nervous structures. The rate of calcium fall, and not so much its absolute concentration in the serum, is related to the onset of parathyroid deficient symptoms but seems to bear no relationship to the type and severity of symptoms initially manifested. As a rule both P/Ca ratios largely varied opposite to the calcium change and at the time of death or when symptoms of parathyroid deficiency appeared were increased by 90 to 300% (inorganic P/Ca) and 60 to 150% (T.A.S.P./Ca) above the normal. Two out of 12 thyroparathyroidectomized dogs, none of which were treated, made a complete recovery though the blood picture and clinical symptoms were identical to those that died of parathyroid deficiency (high inorganic P and T.A.S.P. and low serum calcium accompanied by mild tetany and severe depression). It is concluded that the behavior of the calcium and acid soluble phosphorus compounds in the blood of dogs suffering from parathyroid deficiency is largely due to a disturbance of phosphocreatin metabolism within the muscle fiber (and perhaps other tissues) which greatly involves the Ca/K ratio, thereby affecting also the permeability and irritability of tissues whereby metabolites otherwise non-toxic occur in excess and gain access to the cellular protoplasm which results in the various clinical manifestations found in parathyroid deficiency. The marked increase of the blood P compounds in early and severe parathyroid deficiency and parathormone over-dosage is attributed to the increased destruction of tissue proteins and a terminal retention.—Authors' Summary.

**Parathyroids and fluoride hypocalcemia (Paratiroides e hipocalcemia fluorica).** Gerschman, Rebeca, Rev. Soc. argent. biol. 6: 25. 1930.

Intravenous injection of sodium fluoride (30 mgm. per kgm.) in dogs produces a maximum lowering of calcemia in two hours (3.3 mgm. % average) with a gradual rise from the third hour. Parathyroidectomized dogs did not show the secondary rise.—J. T. Lewis.

**Parathyroids and hypercalcemia (Paratiroides y curva hipercalcémica).** Gerschman, Rebeca, Rev. Soc. argent. biol. 6: 35. 1930.

Blood calcium curves following  $\text{CaCl}_2$  injection are identical in (1) normal, (2) recently parathyroidectomized dogs and (3) animals operated on the previous day, except that the descending curve is somewhat more rapid in (2) and slower in (3).—J. T. Lewis.

**The function of the parathyroids in the light of the pathological physiology of the organ (Die Funktion der Epithelkörperchen im Lichte der pathologischen Physiologie des Organs).** Gold, E., Klin. Wchnschr. 8: 2247. 1929.

Preceding physiological work has established the function of the parathyroid hormone as the maintenance of the levels of serum calcium and phosphorus and of the rate of excretion of calcium. Tetany has been identified as due to a failure of this function. Erdheim recognized the frequency of parathyroid enlargement in osteitis fibrosa cystica and osteomalacia and attributed the change to compensatory hyperplasia. Mandl (1925) and Gold (1927) removed parathyroid tumors in patients with osteitis fibrosa cystica and observed a marked clinical improvement together with a decline of the high blood calcium and an abatement of the urinary calcium loss. A summary of the confirming authors is given. Osteitis fibrosa cystica is therefore hyperparathyroidism in opposition to tetany, which is hypoparathyroidism. Withdrawal of bone deposits through long continued injections of parathyroid extract is demonstrable experimentally. Careful studies of calcium and phosphorus relationships should now be made on such other conditions as myasthenia gravis and paralysis agitans which have been held to be of parathyroid origin.—Allan T. Kenyon.

**Parathyroid hormone and calcium metabolism (Studien über das Epithelkörperchenhormon und den Kalkstoffwechsel).** Inaba, M., J. Biochem. 12: 35. 1930.

Oral administration of parathyrenin to rabbits had no effect on the blood calcium (Kramer and Tis, all method). Subcutaneous administration (0.8-1.0 cc. per kilo) produced a transitory hypercalcemia: intravenous injection

(0.2-0.3 cc. per kilo) produced a hypercalcemia of about 24 hours duration. Simultaneous injection of 1%  $\text{CaCl}_2$  solution (5 cc. per kilo) increased the duration of the hypercalcemia to 140-166 hours. Calcium chloride alone caused only a 20-28 hour hypercalcemia. Atropin and pituglandol, injected with calcium chloride solution, increased the duration of the hypercalcemia, but not as definitely as parathyrenin. The increased blood calcium level was accompanied by a nearly parallel change in blood phosphorus (inorganic—Bell and Doisy method) and by increased excretion of calcium in urine and feces. —B. S. Walker.

**Production in guinea pigs of fibrous bone lesions with parathyroid extract.** Jaffe, H. L., A. Bodansky and J. E. Blair, *Proc. Soc. Exper. Biol. & Med.* 27: 710. 1930.

In guinea pigs subcutaneous injections of parathormone regularly produced the bone changes typical of *ostitis fibrosa*, including the appearance of new bone a few days after cessation of the treatment.—M. O. L.

**The effect of vitamin D and of reaction of diet upon response to parathyroid extract.** Morgan, A. F. and E. A. Garrison, *J. Biol. Chem.* 85: 687. 1930.

Experiments on 28 dogs, the majority of which had been kept on a known diet since weaning, indicate that vitamin D and alkaline reaction of diet, together or separately, increase the susceptibility to injection of parathyroid extract. Dogs reared on artificial diets (Ca: P ratio 1.18 to 1.64) without vitamin D, respond but little to parathyroid extract. Similar dogs, given vitamin D, show abnormally large increases in serum Ca and inorganic P, together with fatal symptoms of overdosage. Dogs given diets of normal Ca: P ratio, low in P and Ca, with or without vitamin D, respond with similar toxic symptoms to parathyroid extract, if sufficient sodium carbonate is given to make the urine alkaline. Administration of ammonium chloride has little effect on the response to parathyroid administration.—B. S. Walker.

**The relief of parathyroid tetany by injections of uranium nitrate.** Swingle, W. W., *Physiol. Zööl.* 1: 496. 1928. *Abst. Biol. Absts.* 3: 1207. 1929.

Recent studies have shown that slight changes in the acid-base equilibrium, with a shift in the reaction of the blood toward the acid side, exert a profound effect upon the tetany of parathyroid insufficiency. Uranium nitrate is a powerful nephrotoxic agent, and when injected into a normal or parathyroidectomized dog produces a marked acid intoxication. The acidosis appears to be due to retention of phosphate and sulphate ions and probably also some organic acid. Parathyroidectomized dogs exhibiting violent tetany symptoms have a normal acid-base equilibrium. Following injection of uranium nitrate, the  $\text{CO}_2$  capacity,  $\text{CO}_2$  content, and pH of the blood drop, and accompanying the shift of the reaction of the blood to the acid side, the tetany symptoms disappear. The dog remains free from tetany for a week or ten days, plays about in normal fashion, and eats heartily. Tetany again supervenes when the acid-base equilibrium returns to normal. The serum Ca increases slightly following injection of uranium nitrate. The answer to the question why changing the reaction of the blood toward the acid side brings about cessation of tetany symptoms and small increases in the serum Ca is probably that the increased hydrogen-ion concentration renders the serum Ca (a certain fraction of it) more diffusible and also takes care of any excess of P which may be present by stimulating its excretion.

**Influencing callus formation in bone fractures (Experimentelle Beeinflussung der Callusbildung bei Knochenfrakturen).** Glassner, K. and J. Haas, *Klin. Wchnschr.* 7: 1633. 1928.

Experiments in the literature in regard to the effects of the thymus on bone healing may be divided into two groups: (1) the effect of thymus extirpation; (2) the effect of injection or feeding of thymus extracts. The authors working with cats report that removal of the thymus leads to deficient callus formation. Also, that thymectomized cats injected with thymus extracts plus phosphorus show a more vigorous callus formation than control animals with fractures in which the thymus is intact. Applying these results to human material, they report that after osteotomy for bow legs, thymus extracts hastened callus formation.—H. L. Jaffe.



was relieved by thyroid and remained well on thyroid. Two years later he developed a true clinical picture of pernicious anemia. He was put on liver treatment. Thyroid was omitted at this time and the metabolism went to -40 and he showed myxedematous changes. In three of our cases the pernicious anemia appeared first; in the others, myxedema was present first. The two may coexist and both may be cured by the appropriate treatment. The necessity of thyroid treatment should be kept in mind in any case of anemia.

**Effect of thallium acetate on the basal metabolism of rats.** Mu, J. W. and C. K. Hu, *Proc. Soc. Exper. Biol. & Med.* 27: 251. 1930.

In four rats injected with thallium acetate in doses of 12 and 8 mgm. per kilo, there was a transitory but definite decrease in the basal metabolic rate. Since thallium acetate causes degenerative changes in the thyroid gland, the authors attribute the variations of the metabolic rate to an action of the thallium on the thyroid.—M. O. L.

**Athyreosis with few symptoms, together with a consideration of the toxic action of irradiated ergosterol** (Über athyreose nebst einige Befunden, betreffend die Frage von der toxischen Wirkung des bestrahlten Ergosterins). Nikoloeff, N. M. and Z. W. Zimbler, *Jahrb. f. Kinderh.* 126: 222. 1930.

Complete absence of the thyroid gland in a child of one year of age was not accompanied by any symptoms, according to the authors, of athyreosis or myxedema. A study of the case report, however, reveals some symptoms which may be placed upon a hypothyroid basis, such as underweight and undergrowth, saddle nose, edema of lids, thick lips, umbilical hernia, thickened tongue, large fontanelle, absence of teeth, and a dry, edematous skin. There were no myxedematous pads in the supraclavicular region. The child had always been a weakling from birth. Several chemical studies of the blood were made but the findings cannot be accepted as being due to the athyroid condition as the child had in addition a multiplicity of conditions such as bilateral otitis media suppurative, purulent meningitis, double pneumonia, noma, subacute entero-colitis and sepsis. Post mortem examination of the endocrine organs showed an atrophic state of the thymus, hypophysis, adrenal, pancreas and parathyroids. There were no evidences of hypertrophic compensatory processes in any endocrine glands. There was no apparent increase in thyroïdin following the administration of irradiated ergosterol. The authors feel that some of the symptoms present could be attributed to the toxic action of the ergosterol in the light of a hypercalcemia.—M. B. G.

**Interchange of ionized and biological iodine** (Die Transformation von ionisiertem und biologischem Jod). Pfeiffer, G., *Biochem. Ztschr.* 215: 197. 1929.

Two unilaterally thyroidectomized dogs were fed iodine, one in the form of KI, the other in iodized radish leaves. Comparative analyses were made of the extirpated half-gland, of urine and feces during the experiment, and of the residual thyroid tissue after the experiment. The dog fed with KI retained more iodine in the tissues as a whole, but the dog fed with the "biological" iodized material had a higher iodine concentration in the thyroid gland, with a greater absolute and relative increase in iodine content of the thyroid as compared with the initial analysis.—B. S. Walker.

**Basal metabolism studies in normal pregnant women with normal and pathologic thyroid glands.** Plass, E. D. and W. A. Yoakam, *Am. J. Obstet. and Gynec.* 18: 556. 1929.

The basal metabolic rate shows an increase during normal uncomplicated pregnancy of approximately 15%, with a fall to normal in the first few days after delivery. A greater rise with slower fall to normal suggests increased thyroid activity incident to pregnancy. A small percentage of women with clinically normal thyroid glands have a metabolic rate which rises above plus 20%. Patients with palpable thyroid disease show a greater tendency toward such high rates, the incidence rising to 35% with small colloid and adenomatous goiters, and to 50% in the large colloid type. This is taken to indicate that pathologic thyroid glands are less able to respond normally to the demands of

gestation, but tend to function abnormally and so to produce symptoms of hyperthyroidism. Iodine, given prophylactically during pregnancy, is apparently unable uniformly to prevent gestational hypertrophy of the normal thyroid gland, but seems to be quite effective in preventing such a change in glands which are pathologically altered when pregnancy begins, and may actually lead to a reduction in the size of certain colloid goiters. Iodine given to pregnant women acts very effectively to prevent the appearance of congenital goiter in the newborn.—Authors' Summary.

A direct physiological demonstration of the existence of a thyroid hormone which regulates the excitability of the psycho motor centers (*Démonstration physiologique directe de l'existence d'une hormone thyroïdienne régulatrice de l'excitabilité des centres psycho-moteurs*). Regnier, J., D. Santenois, P. Vare, H. Verdier and M. Vidacovitch. *Rev. franç. d'endocrinol.* 8: 26. 1930.

Blood was collected from the thyroid veins of dogs and the serum injected into experimental animals. The chronaxie of the motor cortex (sygmoïd gyrus) was determined by the Lapique method before and after injection. The decreased chronaxie resulting is cited as direct evidence that the thyroid gland secretes a substance that causes increased irritability of the cerebral cortex. Significantly positive results were obtained, however, only in dogs that were "vagotonic," i. e., giving a strongly positive oculo-cardiac reflex. It is deduced, therefore, that the vagus nerve has a regulatory influence via the thyroid on cortical excitability. The deduction is confirmed by the effect of high section of the vagus which, by cutting off access to the thyroid, leads to decreased cortical excitability. Similarly, increased cortical excitability was shown to follow small doses of eserine or electric stimulation of the vagus fibres to the thyroid; this is ascribed to hyperthyroidism thereby induced. Thyroidectomy was found to lessen and thyroid extract, to increase the cortical excitability. Under more favorable conditions of thyroid activity an exciting effect of carotid blood upon the cortex could be demonstrated.—R. G. H.

Cholesterol metabolism in relation to thyroid and spleen (*Untersuchung über Cholesterinstoffwechsel in seiner Abhängigkeit von Schilddrüse und Milz*). Sakai, H., *Biochem. Ztschr.* 216: 32. 1929.

The average cholesterol content of the livers of three normal guinea pigs was 0.188%, of the suprarenals of five normal guinea pigs, 4.338%. Following thyroid feeding, three guinea pigs gave cholesterol percentages of 0.247 in the livers and 7.329 in the suprarenals (averages). The cholesterol was determined gravimetrically as the digitonid. Following removal of the spleen from fifteen guinea-pigs, variations above and below the normal range of cholesterol content of liver and suprarenals were observed, both in the normal group and in the thyroid-fed group.—B. S. Walker.

Thyroglobulin versus thyroxin. Schulhof, K., *Am. J. Physiol.* 93: 170. 1930.

The presence of thyroglobulin in the lymph and blood from the thyroid gland has been established, while there is no evidence for the actual secretion of free thyroxin. It is possible that the latter is split off from the thyroglobulin in the blood or organs, but thyroglobulin may have other active groups than thyroxin. Injections of foreign thyroglobulin in rats have a marked action on the basal metabolic rate and on the weight. When injected in doses equivalent in their iodine content with thyroxin, the action of thyroglobulin is of the same order, at least within the quite large limits of the probable error of the methods used. Other methods which seem to be more promising are discussed.—Author's Summary.

The Arneth count in normal and in thyroidectomized sheep. Simpson, Ethel D., *J. Exper. Physiol.* 19: 309. 1929.

There was a displacement of the Arneth count to the right which appeared two or three weeks after operation and persisted for three to four weeks. —C. I. R.

The sedimentation rate of the erythrocytes as a diagnostic and therapeutic index in thyroid disturbances (*Die Senkungsgeschwindigkeit der Erythrocyten als Diagnosticum und therapeutischer Masstab bei Schilddrüsenerkrankungen*). Taterka, H., and C. H. Goldmann, *Klin. Wchnschr.* 9: 303. 1930.

The sedimentation rate of the erythrocytes is a simple and reliable method of determining functional disturbances and results of treatment of thyroid disturbances, particularly Basedow's disease. The results of roentgenotherapy can be so determined, as can the results of attention to patients with hypothyroidism. In Basedow's disease a lessening of the rate of sedimentation runs parallel with a lessening of toxicity. In hypothyroidism there is a retardation of the rate of sedimentation as compared to normal. Iodine administration is likewise capable of varying the sedimentation rate.—I. B.

# ENDOCRINOLOGY

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### THE ROLE OF THE PITUITARY POSTERIOR HORMONE IN FAT METABOLISM

W. RAAB, M.D.  
PRAGUE, VIENNA

Many authors [Bailey and Bremer (1), Camus and Roussy (2) and others] deny any importance of the hypophysis for the physiological regulation of fat metabolism and for the development of obesity since the symptoms that are frequently ascribed to pathological changes of the hypophysis can be fully reproduced by experimental injury of the base of the midbrain and especially of the tuber cinereum. The work of Cushing (3) and Biedl (4) and others suggests, however, that there is a very close relationship between the pars intermedia and posterior lobe of the hypophysis and the mesencephalon not only in local but also in functional respect. Biedl assumes a stimulating action of the middle and posterior lobe hormone upon certain metabolism centers in the midbrain.

A long series of experiments that I (5) have carried out in dogs shows that pituitrin regularly exerts a definite effect upon the fat content of the blood. While the blood fat (petrol-ether-fraction) usually rises during fasting, pituitrin causes on the contrary a fall which, as it has also been shown by Blix and Ohlin (6), is due to a diminution or even complete disappearance of the circulating neutral fat. This reaction lasts for several hours and the normal level is reattained within about twenty-four hours. Doses of several cubic centimeters are needed to produce the effect if given by subcutaneous injection, while much smaller amounts (about 1/10 of the subcutaneous doses) are fully effective if injected into the brain ventricles, thus demonstrating the local action of pituitrin in the midbrain. The pituitrin effect disappears after mechanical destruction of the tuber cinereum or after administration of drugs that paralyze the mesencephalic centers (pyramidon, antipyrin, aspirin). It is also absent after transection of the cervical spinal cord, after section of the abdominal splanchnic and after paralyzing the sympathetic nervous system with ergotamin. The depressant action of pituitrin upon the phospholipoids of the blood [Blix and Ohlin (6)] I have recently found to be lacking or at least weakened in Professor Cannon's completely sympathectomized dogs (5c).

Various authors [Coope and Chamberlain (7), Oshima (8), Steppuhn and collaborators (9)] have observed an accumulation of fat in the liver following injection of pituitrin, which also lasts for several hours and then disappears again. At the same time the peripheral tissue fat diminishes temporarily [Steppuhn and collaborators (9)].

A survey of these experimental facts gives clear evidence that the pituitrin posterior lobe hormone has doubtlessly a definite influence upon fat metabolism and it seems justified to draw the conclusion that pituitrin favors the absorption of circulating fat by the liver by a nervous path starting in the tuber cinereum and ending in the liver. If one assumes a certain quantity of fat to be thus normally destroyed within the liver tissue it is evident that any disturbance in the cooperative activity of the "pituitary mesencephalic system" will leave these fat amounts undestroyed. They will be stored in the tissues and consequently lead to obesity.

There is a striking parallelism between the mechanism of the so-called chemical heat regulation and the mechanism of the action of pituitrin in fat metabolism. Both of them have their nervous center in the tuber cinereum, both of them are abolished by antipyretic drugs acting upon these centers, both of them are abolished by section of the cervical spinal cord [Freund and Grafe (10)] and abolished or weakened by sympathectomy [Cannon (11)] and by ergotamin [Rigler and Silberstern (12)]. Hypophysectomy damages the heat production; this can be restored, however, by the administration of pituitrin [Hashimoto (13)]. Subjects of pituitary obesity frequently have a lowered body temperature [Cushing (14)]. It seems, therefore, not impossible that the physiological significance of the action of pituitrin would be an intrahepatic oxydation of fat contributing to the maintenance of heat production.

As an illustration of the possibility of development of obesity by pure pituitary lesion there might be mentioned a case that I observed in Professor Biedl's Clinic in Prague. A male patient, 31 years old, was healthy until two weeks before admission. Within this latter time headaches, loss of sexual potency, and sudden rapid development of obesity in the face, on the abdomen and on the hips was noted. An increase in weight of ten kgm. occurred. The abdominal skin showed large dark reddish striae each about three inches wide. There was a slight erosion of the anterior wall of the sella. There were eye symptoms. The patient died a few weeks later of septicemia deriving from a phlegmon. The hypophysis was macroscopically scarcely enlarged. Histologically there was found, however, a very small basophile adenoma which had almost entirely taken the place of the posterior lobe. The neighboring nervous regions were intact. This case of an "acute" pituitary obesity is perhaps the only one described in which any participation of the tuber cinereum, etc., can be ruled out with certainty.

On the other hand, there are known cases of purely mesencephalic

obesity caused by encephalitis, tumors, hydrocephalus, etc., without any lesion of the hypophysis.

Any attempts to treat cases of this latter kind with pituitrin must fail because of injury and inactivity of the responding nervous organ. Also in purely hypophyseal or other cases of obesity one cannot expect any considerable therapeutic effect of pituitrin since the subcutaneous route offers no possibility of contact with the midbrain tissue in effective concentration, while the adequate intracranial way is not, of course, suitable for a continuous treatment. Besides, pituitrin does not seem to remove fat after it is once deposited in the tissue stores. A comparison of the arterial and venous fat content of the limbs does not show a definite mobilizing effect of pituitrin [Raab (5)].

I want to emphasize the remarkable parallelisms between the adreno-sympathetic and the pituitary-mesencephalic systems. In both we see a mutual cooperation of an endocrine "gland" which as a matter of fact is not a real gland but an organ deriving from nervous tissue and acting through its hormone specifically upon its respective nervous mother-tissue. In both cases there is a local and probably also functional relationship with a neighboring real glandular structure: the adrenal cortex and the pituitary anterior lobe. Both hormones, adrenalin and pituitrin, show a series of similar actions on the vascular system and on smooth muscle, both of them influence metabolism and heat regulation apparently in a definite way.

#### SUMMARY

Large subcutaneous or smaller intraventricular doses of pituitrin decrease the neutral fat content of the blood. The reaction is abolished by mechanical destruction or pharmacological paralysis of the centers in the tuber cinereum, after transection of the spinal cord, after paralysis or section of the abdominal splanchnic, or after paralyzing the latter with ergotamine, or after phosphorus poisoning. An accumulation of fat in the liver and a decrease of the peripheral tissue fat has been noted after pituitrin injection. The conclusion is drawn that pituitrin promotes the absorption and destruction of circulating fat by the liver through a nervous pathway starting in the tuber cinereum and running through the cervical spinal cord and the abdominal splanchnic to the liver. Any disturbance of the cooperative pituitary-mesencephalic system would lead to a retention of excess fat amounts in the body and thus lead to obesity. Comparative arterio-venous fat determinations suggest that pituitrin does not affect deposit fat directly. There seems to be a close relationship between the pituitrin-nervous mechanism for fat destruction and the so-called chemical heat regulation. Verified cases of purely hypophyseal and purely mesencephalic obesity have been observed by the author.

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## ESTROGENIC SUBSTANCES. II. AN ANALYSIS OF PLANT SOURCES

BURNHAM S. WALKER, Ph.D. and JAMES C. JANNEY, M.D., F.A.C.S.

From the Evans Memorial and Boston University School of Medicine  
BOSTON

An interesting by-product of the study of the female sex hormones was the observation that substances capable of initiating estrus in the castrated female mouse could be obtained from certain plant tissues as well as from the reproductive and other tissues of animals.

Following the introduction by Allen and Doisy (1923) of the vaginal smear method of testing for the presence of estrogenic material, Loewe, Lange and Spohr (1927) investigated several flowering plants, with positive results. Fellner (1926) reported an active extract from grains of rice and wheat. Using their chromaphil reaction as a test method, in addition to uterine growth and the vaginal smear, Dohrn, Faure, Poll and Blotvogel (1926) obtained positive results with a group of plant materials, including beet seeds, potatoes and yeast. Glimm and Wadehn (1928) made a thorough investigation of yeast extracts, from both brewer's and compressed yeast, with positive results. In his recent monograph, Frank (1929) notes a positive extract obtained from cooked potatoes. With extracts of tomato juice and of bacterial cultures (*B. coli* and *B. pyocyaneus*) he obtained (in collaboration with Goldberger and Gustavson) strictly negative results.

This present study was begun with the intention simply to study a variety of plants and plant products with respect to their content in estrogenic material. During the course of the study we have been able to observe certain indications of a relationship between estrogenicity and the portion of a plant used as a source of extract, and also with the age of the plant tissue in question and the rate of its growth.

Our extracts were prepared by one or the other of two type procedures: alcohol extraction and chloroform extraction.

Alcohol extraction was carried out by allowing the fresh material to stand covered with 95 per cent alcohol for a period of several days at room temperature. The liquid was then pressed from the solid portions and evaporated to small volume. Cheese-cloth was used to strain out the solid material; filter paper is not advisable on account of its tendency to adsorb the active material (Laqueur, Hart and de Jongh, 1926). The sludge remaining after evaporation of the alcohol was made alkaline with sodium carbonate and extracted with ether. (With material which tended to emulsify with ether sufficient anhydrous sodium carbonate was added to take up all the water.) The residue remaining after evaporation of the ether was taken up in physiological salt solution and injected. (In a few



cases where the residue was distinctly oily, oil of sesame was used as the injection vehicle.)

Chloroform extraction was carried out in the tissue extractor described in our previous communication (Janney and Walker, 1930). The chloroform was then separated from the solid material, evaporated and the residue treated with alkali and extracted with ether as described above. The remainder of the procedure was the same as for the alcohol extract.

The technique of the mouse tests was the same as used by us heretofore and described in previous papers (Janney, 1929; Janney and Walker, 1930).

The majority of the plant materials proved negative when their extracts were injected into castrated white mice. The negative results are summarized briefly in Table I.

TABLE I

Material	Type of Extraction	Maximum Number of Grams of Original Tissue per Dose	Number of Mice Used
Apples	Alcohol	200	6
Beets	Alcohol	200	8
Cabbage	Alcohol	500	10
Carrots	Alcohol	500	5
Carrots (young)	Chloroform	300	10
Corn	Alcohol	500	6
Grapes	Alcohol	500	5
Peaches	Alcohol	500	6
Plums	Alcohol	500	6
Potatoes	Alcohol	200	12
Spinach	Chloroform	200	20
Sweet Potatoes	Alcohol	500	6
Swiss Chard	Chloroform	200	24
Tomatoes	Alcohol	133	6

In the experiments summarized above, the materials were in all cases (except the young carrots) mature and obtained from market or garden in the form usually sold for food purposes. The tops were removed from the root vegetables, the corn was cut from the cob, the peaches and plums were stoned before weighing. Weights refer to fresh tissue before extraction.

In addition to the above plant extracts, solutions or suspensions of certain plant constituents were injected and found negative. The substances so tested were carotin, chlorophyll, inositol, phytin, saponin and urson.

A certain limited number of experiments, on the other hand, yielded definitely positive results.

*Alder leaves and catkins.* These were collected in early spring and extracted with alcohol. Male and female catkins were collected and extracted separately. The leaves of the alder were also collected at the same time and extracted.

*Willow catkins.* These were collected later in the season and extracted with alcohol, male and female catkins separately. A small percentage of positive reactions was observed.

*Sprouted oats.* The oil obtained by chloroform extraction of 20 grams of oats after sprouting was sufficient to initiate estrus in a castrated mouse. The oil from 100 grams of unsprouted oats failed to bring about any reaction.

*Rhubarb leaves.* Collected in May. Extracted with chloroform. Positive reactions with large doses.

The more detailed experimental results with these positively reacting extracts are given in Table II.

TABLE II

Material	Grams Original Tissue per Dose	Number of Mice	Number Positive	Number Negative
Alder Catkins.....(male).....	160	1	1	0
	80	3	3	0
	20	1	1	0
(female).....	20	3	3	0
Alder Leaves.....	30	6	3	3
	20	1	1	0
Willow Catkins.....(male).....	50	1	1	0
	20	5	0	5
	20	5	1	4
(female).....	12	1	1	0
Oats.....(unsprouted)....	150	12	4	8
	100	6	0	6
(sprouted).....	100	4	4	0
	50	4	4	0
	25	4	4	0
	20	2	2	0
	10	2	0	2
Rhubarb Leaves.....	200	4	4	0
	100	5	3	2

(Smaller doses all negative.)

From the above results it appears that a relatively high concentration of estrogenic material occurs in plants:

1. Associated with green pigmentation. Roots or tubers of plants were in our experiments strictly negative (contrast Dohrn, Faure, Poll and Blotvogel, 1926). Even young growing roots were negative, as shown by the chloroform extract of very small carrots, which was negative in amounts corresponding to 300 grams. Fruits were entirely negative. The presence of estrogenic material in yeast (Glimm and Wadehn, 1928) should be mentioned as an outstanding exception to this generalization.

2. Coincidentally with rapid growth. Green parts of plants which had passed the phase of rapid growth were also negative (see Table I). All

the positive extracts were obtained from plants in the early spring when growth is most rapid, except in the case of the sprouted oats, where a similar condition of rapid growth was artificially induced.

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# RECENT OBSERVATIONS ON THE IODINE REACTION IN EXOPHTHALMIC GOITER\*

WILLARD OWEN THOMPSON AND PHEBE K. THOMPSON

From the Department of Medicine, Rush Medical College,  
and

The Presbyterian Hospital

CHICAGO

Our observations may be summarized under three main headings:

1. The range of effective iodine dosage.
2. Refractoriness to iodine.
3. Prolonged treatment by iodine alone.
4. Myxedema during the administration of iodine.

## THE DOSE OF IODINE

While working in the thyroid clinic of the Massachusetts General Hospital in Boston, we made an attempt to determine the smallest dose of iodine that will produce any reduction in basal metabolism and the smallest amount that will produce a maximum reduction. For this purpose we observed the effect on basal metabolism of the daily administration of about 6 mgms.† of iodine (roughly, one drop of the compound solution), 3 mgms., 1.5 mgms. and 0.75 mgm. to four series of hospital patients with exophthalmic goiter and compared the effect with that of much larger doses given initially (1) (2) (3) (4). The routine was to wait until a stationary level of basal metabolism was reached. Compound solution of iodine in one of the doses mentioned was then administered and daily observations of the metabolism were made. When the metabolism again reached a level, much larger doses (usually 30 minims daily) were given and their effects noted.

The reduction in basal metabolism during the daily administration of 6 mgms. of iodine appeared to be as great as that noted by Starr, Segall and Means (5) in the same clinic, during the daily administration of about 126 mgms. (roughly, 1 cc. of the compound solution).

During the daily administration of 6 mgms., 88 per cent of the cases showed a reduction in basal metabolism of 10 or more points; during the daily administration of 3 mgms., 65 per cent; during the daily administration of 1.5 mgms., 50 per cent; and during the daily administration of 0.75 mgm., 33 per cent.

The average response in the 6 mgm. series was 27 points (from plus 46 to plus 19 per cent); in the 3 mgm. series it was 14 points (from plus 40 to plus 26 per cent); in the 1.5 mgm. series it was 9 points (from plus 43

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†The amounts of iodine recorded in this article are approximate, owing to the rough method of measurement (1).

to plus 34 per cent); and in the 0.75 mgm. series it was 4 points (from plus 39 to plus 35 per cent).

Between a daily dose of 0.75 mgm. of iodine and one of 6 mgms., the relation between the percentage approach of the basal metabolism towards the normal level and the daily dose of iodine appeared to be roughly a straight line.

The dose of compound solution of iodine commonly employed in the treatment of exophthalmic goiter is about 30 to 45 minims daily, roughly, 250 to 375 mgms. of iodine. Compared with this, 6 mgms. a day might appear too small a dose to be effective. However, compared with the normal rate of iodine utilization, it is large. Boothby et al. (6) have shown that the basal metabolic rate of a "thyroidless individual" may be maintained at a standard normal level by an average daily intravenous dose of 0.25 mgm. of thyroxin, an amount which contains 0.16 mgm. of iodine. From Boothby's observations, it follows that the normal thyroid gland probably does not elaborate thyroxin at a rate faster than 0.25 mgm. daily, and there are reasons for believing that the actual rate may be less than this. (7). Moreover, from analyses of various foods, it seems probable that most people with normal thyroid glands do not ingest as much iodine as this. Thus 6 mgms. of iodine roughly represents at least 35 times the amount which is daily broken down by a normal gland in the form of thyroxin.

We wish to make it clear, however, that this dose is not recommended for the routine preoperative and postoperative treatment of exophthalmic goiter. We have observed patients who failed to show a maximum response to this dose initially, and have seen patients in whom more was required to produce a maximum effect as refractoriness to iodine was developing. Just what the largest dose that is ever required to produce a maximum effect may be, has not been determined. That it is much less than the 30 to 45 minims of the compound solution commonly employed in the routine treatment of the disease appears probable. Certain observations suggest that it is not more than 30 mgms. a day (roughly, 5 drops of the compound solution) (1) (2) (3). For the present, it is our impression that a dose at least this large should be used in the routine treatment of the disease. We know of no contraindications to much larger doses except their unpleasant taste and occasional gastro-intestinal disturbances.

A question that naturally arises is whether the minimum amount of iodine that will produce a maximum reduction in basal metabolism is any different in a goitrous area from that in Boston, a non-goitrous area. In an attempt to solve this problem we have begun a study of the disease in Chicago. Thus far, two patients have shown a well marked reduction in basal metabolism during the administration of 6 mgms. daily and one subject, no response either to 6 mgms. or to 250 mgms. daily administered immediately afterwards. While there may prove to be a difference between the two regions, it would seem that this difference is not likely to be a striking one.

The data also suggest that sufficient iodine must be administered in a sufficiently short time for a maximum storage of colloid to occur. It appeared from the figures of Marine and Lenhart (8), Wilson and Kendall (9), Weir (10) and Cattell (11) that 6 mgms. a day might be just about adequate for this result if most of it could be used for the storage of colloid, whereas the smaller doses were inadequate to cause a maximum storage of colloid in the time that the maximum metabolic effects were noted (3) (4). There was thus observed a rough parallelism between the amount of iodine available for storage of colloid and the percentage approach of the basal metabolism towards the normal level.

In five patients the reaction to iodine was a reversible one, the daily administration of about 0.75 mgm. to 3 mgms. of iodine being associated with an increase in basal metabolism and the severity of the disease, and the immediate subsequent daily administration of about 250 mgms. being associated with a decrease in both factors. These observations suggest that, in certain cases, if the amount of iodine administered falls below a certain amount, it may be used by the thyroid to form a still greater excess of thyroxin; whereas, if the iodine intake exceeds a certain amount, it reverses the reaction and causes a decrease of the thyroxin output. This finding is of interest in connection with the observation that patients with non-toxic goiter may begin to suffer from thyrotoxicosis during the ingestion of such small quantities of iodine as those contained in iodized salt.

It appears from this study that a dose of iodine which in itself may be too small to cause any reduction in basal metabolism (e. g., 1.5 mgms. daily) may, in some way, interfere with the effect of much larger doses (250 mgms. daily) administered immediately afterward. This effect was not as striking in the 3 mgm. series and could not be said to have been produced by the daily administration of 0.75 mgm. Whether the amount of iodine in iodized salt is ever sufficient to produce this effect is unknown. In any event, from the standpoint of the routine preoperative treatment of the disease, it would seem desirable to give initially a sufficient amount of iodine to produce the maximum beneficial effects.

#### REFRACTORINESS TO IODINE

Patients may be initially refractory to iodine or may become refractory during its prolonged administration, after showing an initial response.\* The first type of response is probably less common than the second. When patients are refractory, all the peculiar nervous manifestations of the disease are usually marked and the operative risk may be great. If a patient becomes refractory after showing an initial response, omission of iodine for four weeks or longer may be accompanied by the disappearance of the refractoriness. Iodine may then be readministered and operation performed with safety. When the metabolism is rising rapidly during the administration of iodine, it seems to us always wise to

\*Examples of the development of refractoriness are recorded elsewhere (1).

omit iodine and postpone operation. During this period, the patient should be at rest in bed in the hospital. In patients who are initially refractory to iodine the details of treatment have not been worked out.

#### PROLONGED TREATMENT BY IODINE

The response of patients with exophthalmic goiter to iodine is variable, and temporary improvement is not to be considered the only result of long continued medication. While at the Massachusetts General Hospital, we (12) observed the effect of administering iodine for long periods to 24 patients (14 with mild and 10 with severe or moderately severe cases) who had not been otherwise treated. With three exceptions (all unsatisfactory responses to iodine), the patients pursued their daily work throughout the period of observation, thus eliminating the effect of rest. In 9 of the 14 mild cases (64 per cent) the results were satisfactory, i. e., the clinical evidence of thyrotoxicosis was either completely or almost entirely kept under control, and the basal metabolism was kept at a normal level. In 4 of these 9 cases, in which iodine was omitted from ten to sixteen months, the disease had apparently disappeared; and in 3 others, in which iodine had been omitted from four to seventeen weeks, there had been no recurrence of symptoms. In 3 of the 14 mild cases (22 per cent) the results were fairly satisfactory, i. e., there was definite improvement in spite of tardiness or fluctuations in the response. In two mild cases (14 per cent) the results were unsatisfactory. In the 10 severe or moderately severe cases, the results were satisfactory in one (10 per cent); there was no permanent satisfactory benefit in 4 (40 per cent); and the disease became worse in 5 (50 per cent).

At the same clinic we (13) observed the effect of administering iodine for long periods to 27 patients who were thyrotoxic following a subtotal thyroidectomy for exophthalmic goiter. In 3 of these patients little or no reduction of basal metabolism was noted during its administration, and in 3 others, only a temporary reduction. In 18 of the remaining 21 cases the basal metabolism could be held at a more or less constant level for months to years by continuous administration. In 11 of these the level to which iodine thus depressed the metabolism was plus 15 per cent or lower; in 6, plus 16 to plus 20 per cent; and in one case, plus 21 to plus 25 per cent. In 3 cases, the level to which iodine depressed the metabolism was somewhat inconstant and ranged between 0 and plus 33 per cent. In all cases showing only temporary improvement or none at all during the administration of iodine, there was a large amount of palpable thyroid tissue.

These observations suggest that the most important thing in determining the response of patients with exophthalmic goiter to prolonged iodine medication may be the severity of the disease, mild cases commonly responding satisfactorily and moderately severe and severe cases rarely showing more than temporary improvement.

## MYXEDEMA DURING THE ADMINISTRATION OF IODINE

During the administration of iodine to a patient whose basal metabolism is standard normal following a subtotal thyroidectomy for exophthalmic goiter, any one of the following effects may be noted:

1. No response—the most common result.
2. Depression of the basal metabolism to a subnormal level without any accompanying clinical evidence of underfunction of the thyroid gland (14).
3. Depression of the basal metabolism to a subnormal level, in association with the development of myxedema (15) (16).

The latter two types of response are occasionally seen in mild untreated cases of exophthalmic goiter. The third type of response is rare, and so far we have noted it in only three cases following operation and in only two preceding operation. In these patients 1.5 to 4.5 months elapsed from the time the iodine was started until the basal metabolism dropped from a standard normal level to its lowest point and myxedema developed. The myxedema could be made to disappear either by omitting iodine or by continuing iodine and giving thyroid in addition. Both procedures produced the same clinical picture. The development of myxedema during iodine administration is not confined to the immediate postoperative period, but may occur years after operation. The patients who developed myxedema following operation appeared to be in a healthy state when their basal metabolism was normal and they were not receiving iodine. A diminution in heat production has occasionally been produced by administering iodine to patients who have never suffered from exophthalmic goiter (17) (18) and to normal animals (19) (20) (21).

Thus, so far as can be determined clinically, the myxedema which occasionally develops during the administration of iodine to patients who have a normal basal metabolic rate following a subtotal thyroidectomy for exophthalmic goiter, is due to an inhibition of the secretion of the normal thyroid hormone. This suggests that iodine may cause a reduction in the high basal metabolism of exophthalmic goiter in the same manner.

## SUMMARY

In Boston the smallest amount of iodine that will produce any reduction in basal metabolism in exophthalmic goiter is greater than 0.75 mgm. daily in about two-thirds of the cases. The minimum amount that will produce a maximum reduction is roughly 6 mgms. daily in the majority of cases. Between these two limits, the relation between the percentage approach of the basal metabolism towards the normal level and the size of the dose is roughly linear. The effective dose has not been determined in Chicago, but it is known that 6 mgms. a day will cause a reduction in basal metabolism in some cases.



Iodine must be administered at a certain minimum rate in order for the maximum effects to be produced. It also appears that this rate may be one that is sufficient to cause colloid to be stored at an adequate rate.

In a few cases the reaction to iodine is reversible.

The administration of a small dose such as 1.5 mgms. daily may sometimes interfere with the effect of a much larger dose administered immediately afterward.

In the routine treatment of the disease, it is desirable to give initially an excess of iodine sufficient to produce maximum effects. The amount necessary to do this is undetermined, but probably is not more than 30 mgms. (roughly 5 drops of the compound solution) daily.

In patients who develop refractoriness to iodine, it is wise to postpone operation until iodine has been omitted long enough to allow the refractoriness to disappear.

In a large percentage of mild cases of the disease improvement may be maintained for long periods by iodine, whereas moderately severe or severe cases rarely show more than temporary improvement.

Myxedema may occasionally develop during the administration of iodine to patients who have a normal basal metabolism following subtotal thyroidectomy for exophthalmic goiter and to patients with mild untreated cases of the disease.

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# THE EFFECT OF ANTERIOR PITUITARY EXTRACT ON THE DEVELOPING ALBINO MOUSE\*

GEORGE EDWIN JOHNSON AND ROBERT TOWNER HILL

Kansas State Agricultural College  
MANHATTAN, KANSAS

## INTRODUCTION

The present paper extends anterior pituitary injection work in this laboratory with rats (1) to mice, and stresses the effect upon the male genital system. The work of Evans and associates (2, 3, 4, 5, 6) on rats, of Robertson and Ray (7) on mice, and of Putnam, Teel and Benedict (8) on rats and dogs have shown a stimulation of growth from injected extracts of this gland. Similar influences have also been indicated by other work on hypophysectomized rats (9, 10, 11), on thyroidectomized rats (12), and on castrated rats (13, 14). Evans and Long (2, 3) reported inhibition of oestrus and excessive lutein formation in female rats from such injections and similar results have been obtained by Johnson and Sayles (1). Stimulation of sexual development on the other hand has been produced by transplant methods (9, 15, 16, 17) and by extracts prepared from urine of pregnant women (18, 19, 20). Fertility in male rats appeared at first not to be affected by anterior pituitary injections (21) but later work indicated a loss of sexual interest in such rats (5, 19). Engle (22), however, showed enlargement of sex organs, except testes, of male rats which had been injected with the urine of pregnant women.

## METHODS

The extract used in the experiments reported here was prepared from the anterior lobes of bovine pituitary glands obtained cold from Kansas City, according to the method given by Johnson and Sayles (1). Essentially this consists of an extraction with sodium hydroxide with a later neutralization by acetic acid, followed by filtering.

The young mice were weaned at the age of 20 days, and as nearly as possible half of the animals of each sex were taken as "experimentals" (injected with extract) and the remaining ones were taken as controls (injected with 0.9 per cent saline solution). Injections of 0.1 cc. were made for each of the first five days. If the animals grew well the dose was increased 0.1 cc. every five days until a maximum of 0.5 cc. was injected daily. Weights were taken at five day intervals.

In general, the earlier animals used were injected for 130 days and killed at 150 days of age. In order to learn at what period of life the extract caused changes in size and histological appearance, if any, of the

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\*Contribution No. 131 from the Department of Zoology, Kansas State Agricultural Experiment Station, Manhattan, Kansas.

TABLE I  
EFFECT OF ANTERIOR PITUITARY EXTRACT ON WEIGHT OF FEMALE MICE

Days of Age.....	20	30	40	50	60	70	80	90	100	110	120	130	140	150
Average Weight of Experimental Females in Grams.....	0.7	11.0	14.3	17.6	20.1	21.2	22.7	24.5	25.3	26.0	26.8	26.2	26.5	26.4
Number of Grams Heavier than Controls <sup>1</sup> .....	-0.9	-0.2	0.5	1.5+	1.1+	1.4+	1.5+	3.1-	3.1-	2.3+	2.2	2.0	1.9+	2.4
Number of Experimentals <sup>2</sup> .....	33	33	30	27	24	21	20	18	16	14	11	9	8	8
Per Cent of Experimentals Heavier than Intermediate Controls <sup>3</sup> .....	24	24	21	19	17	15	15	14	12	10	9	7	6	5
.....	3	45	60	78	67 (75)	71	80	94	100	86 (93)	82 (91)	89	88	88

<sup>1</sup>—A plus (+) after a figure indicates that that figure would be greater if corrections were made on account of temporary increases in weight produced by pregnancy. A minus (-) indicates the opposite. A minus (-) before a figure indicates that the figure has a negative value.

<sup>2</sup>—The number of animals decreases with age in Tables I and III because they were killed at different ages for histological study.

<sup>3</sup>—Figures in parentheses give the percentage after corrections are made for temporary weight changes produced by pregnancy.

gonads of both sexes, other animals were killed to give a series from 30 to 150 days of age. Bouin's fluid was used for fixing and Ehrlich's hematoxylin for staining. Measurements were made of the ovaries; testes; body from the tip of the nose to the base of the tail, and from the base to the tip of the tail; and the right hind leg from the anterior edge of the acetabulum to the end of the longest toe. The testes and ovaries were also measured for length, width and thickness and relative volumes roughly computed by multiplying the three dimensions.

The mice were raised from some kindly provided by the Laboratory of Mammalian Genetics of the University of Michigan. Since these mice had been inbred for many generations, less variation would be expected than in a mixed population. Animals of a litter were usually kept in one cage, or sometimes in adjoining cages. All cages were kept under like conditions. Precautions were taken to keep the mice free from internal parasites through cleanliness and by using food which contained no insect intermediate hosts for tapeworms. With two exceptions all the animals were found to be free from internal worm parasites and no external parasites were noticed.

#### RESULTS AND DISCUSSION

##### *Growth of Female*

*Results.* Tables I and II give the pertinent data for females with respect to body weight and body measurements. A study of Table I, and of the original weights which were taken at five day intervals shows that the weights of the anterior pituitary injected females rose from below that of the controls, between 35 and 45 days of age, becoming distinctly higher at 50 days. At 70 days the average difference was 1.42 gm., all females being considered, which, however, is not a statistically significant difference. If those females which had been pregnant at any time during the experiment are eliminated, the difference is 2.16 gm., which is significant ( $D/PE=4.9$ ). At 150 days the experimentals were 2.4 gm. heavier than the controls, a difference which is hardly significant ( $D/PE=3.1$ ), but when animal 2-4, which had been pregnant three times, is omitted the difference in weight, 3.30 gm., is significant ( $D/PE=5.9$ ).

The increased growth of the experimental females took place over the entire body. Table II shows that the experimentals generally had greater

TABLE II  
MEASUREMENTS OF EXPERIMENTAL FEMALE MICE AND COMPARISONS WITH CONTROLS

	Body	Tail	Hind Leg
Average length of all experimental females in mm....	97.2	78.7	31.9
Average greater length as compared with controls in mm.....	3.8	0.0	0.4
Number of experimental females longer than controls	17	12	11
Same lengths as controls.....	0	0	2
Shorter than controls.....	4	7	8
D/E.....	4.2	1.7	1.0

TABLE III  
EFFECT OF ANTERIOR PITUITARY EXTRACT ON WEIGHT OF MALE MICE

Days of Age.....	20	30	40	50	60	70	80	90	100	110	120	130	140	150
Average Weight of Experimental Males in Grams.....	7.0	11.5	15.3	18.8	21.4	22.2	23.7	24.7	25.2	25.2	26.1	23.0	23.4	23.0
Number of Grams Heavier than Controls.....	-0.6	-0.3	0.1	0.5	1.3	1.4	1.9	1.7	2.5	1.8	2.3	-0.1	0.9	1.0
Number of Experimentals.....	26	26	23	20	18	14	12	11	8	4	3	2	2	2
Number of Controls.....	25	25	23	20	18	14	12	10	7	4	3	2	2	2
Per Cent of Experimentals Heavier than Littermate Controls.....	0	62	70	70	78	86	83	73	88	75	100	50	100	100

bone dimensions than the controls. Only the increase in body length, however, appears significant. It was usually more clearly seen in older animals.

*Discussion.* The results showing a moderate increase in growth from the injection are similar to those reported by Johnson and Sayles (1) in the albino rat. The lack of extreme gigantism, such as was obtained in rats by Evans (23), may be due partly to the fact that the experiments reported here terminated at 150 days or less and partly to Evans' use of an extract prepared by centrifugation which may have been more potent for production of growth.

### *Growth of Males*

*Results.* The weights and body measurements of the males included in this study are given in Tables III and IV. At the beginning of the experiment the experimentals averaged 0.6 gms. lighter than those selected for controls, but at the age of 38 days, they averaged more in weight and con-

TABLE IV  
MEASUREMENTS OF EXPERIMENTAL MALE MICE AND COMPARISONS WITH CONTROLS

	Body	Tail	Hind Leg
Average length of all experimental males in mm. . . .	92.8	78.4	31.7
Average greater length as compared with controls in mm. . . . .	3.5	0.8	0.9
Number of experimental males longer than controls	15	10	12
Same length as controls. . . . .	0	2	2
Shorter than controls. . . . .	3	6	4
D/E. . . . .	4.3	1.4	2.8

tinued so to the end of the experiment. At the age of 70 days the injected males averaged 1.42 gm. heavier than the controls, a difference which is not statistically significant ( $D/PE=2.4$ ). At 90 days of age the experimentals were 2.3 gm. heavier than the controls, a difference which approaches significance ( $D/PE=3.17$ ). The figures show a decided increase in growth of the experimental males from the age of 70 to 90 days.

The increase in growth, however, was not as great as in the females. The marked growth at the age of 150 days suggests that the gains may be greater than that of the females late in life. However, the number of males left at the end of the experiment was too small to support a valid conclusion as to this point. As in the case of the females the growth in the experimental males took place over the body and was not limited to the skeleton as shown in Table IV. The differences, however, are small and scarcely significant except for body length, as was the case for the females.

*Discussion.* The present work on male mice confirms the results of Johnson and Sayles (1) with rats. While statistical treatment for any single period does not show the increased growth of either treated male mice or rats to be clearly significant, the fact that the general trend is in that direction, that both experiments showed a positive difference, and the fact that the treated females were significantly heavier than their controls

supplies strong evidence for the belief that the results were not due to chance. This conclusion is supported by the fact that the experimentals were lighter in weight than the controls at first and by the fact that almost without exception they were heavier than their controls after 50 days of age, making the weights at any one age less likely to be produced by chance. It should be noted that Smith and Engle (15, 16) also found that the male rat responded less to anterior pituitary transplants than did female rats, but Evans and Simpson (5) state that males become giants as well as females with their centrifuged extract. The question arises as to whether the growth response of the male is less than that of the female because of the activity of the testes in the male. Would castration permit it to make a more decided response? Evans and Simpson (6) have indicated that the castrated injected male does not gain as rapidly as the normal injected male rat.

#### *Effect on Female Genital System*

*Results.* In both experimental and control females the ovaries appeared to be very similar at the ages of 31, 35, 41 and 50 days, containing many follicles of varying stages but no corpora lutea in all of the six experimentals and in four or five controls. One control 41 days old had a well developed corpus luteum. The chief difference noted was that in the injected animals there was less tendency to form follicular cavities than in the controls. In the medium-sized follicles cavity formation might be absent and in the larger follicles the cavity would usually not be so large as in the controls, indicating the tendency for follicles to change to corpora lutea without the occurrence of ovulation. Corpora lutea were present in the ovaries of three females (two experimental and one control) killed at 55 days of age. They were numerous in the two experimentals but few in number in the control. There were practically as many follicles in the experimentals as in the controls.

In 22 extract-injected females from 65 to 150 days of age, the ovary contained a very large number of corpora lutea and in the older animals it often had a diameter three times as great as that of the ovary of the saline-injected control. There was only one experimental animal which had a smaller number of large corpora lutea characteristic of the normal or control animal of these ages. This animal was pregnant and therefore contained the small number of corpora lutea of pregnancy. A control female 105 and one 150 days old had no corpora lutea. The corpora lutea of the controls had more definite boundaries than many of those of the experimentals, especially where the latter were small and numerous. In animals 65 days or more of age a much smaller proportion of the ovary consisted of follicles in the injected animals than in the controls, but because of the great enlargement of the ovary there was no consistent difference in the actual number of follicles in the entire ovary, judging from counts in one ovary each of six experimentals and of four controls and a general study of the others. Considerable variation was found in both groups.



Not only did the histological evidence indicate that many ova were hemmed in by lutein cells before the follicle could rupture and ovulation take place, but the records show that only four pregnancies (see Table I, 1-1, 6-2, 14-1) were produced in the 28 injected animals that reached the age of 50 days or more. From these there was a total of three mice born; four normal embryos were removed from one female at autopsy, and in another female four embryos, apparently normal, were found at autopsy to be partly resorbed. In the 19 control females, 50 or more days old, there were nine pregnancies and two abortions.

In the study of the ovary slides several ova were discovered in a fallopian tube. This led to a careful study and restudy of the tubes by the senior author and Mr. Richard R. Marsh. Fortunately, the tubes were found present on usually two to four slides of the ovary for nearly all of the females 50 or more days old. Of the 20 experimentals with tubes one to 12 or 23 tubal ova were found in 13 animals, or a total of 88 or 66 tubal ova, depending on whether we include 22 peculiar eggs that appeared more or less vacuolated, shrunken and flattened occurring in one tube. Of the 14 control animals with tubes from three to five tubal ova were found in four animals, or a total of 18 tubal ova. Of the experimentals, therefore, 65 per cent had tubal ova, but only 28 per cent of the controls had them. Tubal ova averaged 4.4 (or 3.3 if the 22 abnormal ova are eliminated) per animal in the 20 experimentals, but only 1.3 in the 14 controls.

The ages at which sacrificed experimentals showed tubal ova were as follows (each number in parentheses indicates the number of ova in one animal): 40 days (5 ova); 70 days (5); 80 days (5); 90 days (12, 5); 100 days (8); 110 days (22); 130 days (9); and 150 days (1, 3, 3, 3, and 10). For the controls the ages and tubal ova were: 80 days (5 ova); 90 days (5); 130 days (5); and 150 days (3).

*Discussion.* The present work shows that in the mouse, as in rats and some other animals considered by others, the formation of lutein bodies is greatly stimulated by anterior pituitary extract such as has been used. Somewhat similar results were obtained with an acid-extracted substance from the anterior pituitary by Larson, Bergeim, Barber and Fisher (24). They suggest that their result might have been produced by the protein content of their extract. The extract used in the present study, however, produced not only lutein formation but in a few cases permitted the formation of normal follicles and ovulation followed by normal pregnancy. More particularly it should be noted that it produced a larger number of tubal ova than were present in the controls. This result can hardly be attributed to some incidental inclusion, but rather to a hormone in the extract. It appears possible, however, that the growth hormone at least is associated with the protein portion of an alkaline extract, for Evans' protein rich centrifuged extract produced more growth than our filtered extract. The fact that both excess lutein formation and increased ovulation giving groups of tubal ova resembling those shown by Smith and Engle (16) were produced by the extract would indicate that our extract contained not

only growth hormone but also the maturity producing hormone usually demonstrated by transplants.

In not showing production of oestrus in immature rats our experiments agree in general with those of Bellerby (25) but not with those of Tecl (26); who claimed to have produced oestrus with alkaline extracts.

### *Effect on the Male Genital System*

*Results:* The size of the testes was not greatly affected by the anterior pituitary extract. Nine experimental animals had larger and eleven had smaller testes (relative combined volume of both testes) than the respective controls. Of these experimentals only three had testes more than 50 cu. mm. (0.05 cc.) larger and only five had testes more than this amount smaller than their respective controls. The total relative volumes of the testes of the experimental animals averaged about 54 cu. mm. (0.054 cc.) smaller than those of the controls. In general these results indicate a slight reduction in size of testes as a result of anterior pituitary injections.

TABLE V  
PREGNANCY OCCURRING IN CONTROL FEMALES MATED WITH NORMAL AND WITH ANTERIOR PITUITARY TREATED MALES

Mated with Normal Males				Mated with Treated Males		
Saline Injected Females	Age in Days When With Normal Males	Number of Days	Times Pregnant	Age in Days When With Injected Males	Number of Days	Times Pregnant With Injected Males
1-1	45-115	70	2	—	—	—
2-4	45-150	105	3	—	—	—
3-4	45-80	35	0	—	—	—
6-4	45-92	47	0	92-120	28	0
6-5	45-92	47	0	—	—	—
12-3	45-62	17	1	62-140	87	*1
13-5	45-57	12	1	57-110	53	0
14-2	45-120	75	1	—	—	—
17-6	45-68	23	0	68-95	27	0
18-6	45-63	18	**1	63-90	27	0
20-7	45-65	20	1	—	—	—
Totals.....	.....	469	10	.....	222	1
Average number of days for each pregnancy.....	.....	46.9		.....	222	

\*Five embryos aborted at half term.

\*\*One embryo aborted at about sixteen days.

The breeding records as given in Table V show a high degree of sterility in the experimental males, since only one pregnancy (five embryos aborted at half term) was produced and this required 222 days as compared with the normal of one litter produced in every 46.9 days.

At autopsy the testes of six of the experimental animals (ages 60, 62, 80, 92, 150 and 150 days) appeared to contain within the membrane surrounding the entire mass of tubules a deposit resembling calcareous material, such as a very thin or "soft" shell abnormally appearing on hen eggs. By probing with a needle this membrane could be broken, but, as it was apparently laid down in the membrane, pieces of it could not be picked off as from a hen's egg. Histological examination later confirmed

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# THE STIMULATIVE EFFECT OF ROENTGEN RAYS UPON THE GLANDS OF INTERNAL SECRETION\*

## A Review of the Literature.

MURRAY B. GORDON, M.D.

From the Endocrine Clinic, Department of Pediatrics,  
Long Island College Hospital

BROOKLYN, N. Y.

Arndt in explanation of experiments with medicinal drugs, expounded the following as a biological concept: "Weak stimuli accelerate vital processes, moderate promote them, strong inhibit them and strongest destroy them" "[Kleine (schwache) Reize fachen die Lebenstatikeit an, mittle starke forden sie, starke hemmen sie, und starkste heben sie auf]." This hypothesis was elaborated by Schultz in 1899 into what now is known as the Arndt-Schultz Law. It has since been extended to serve as the basis for stimulative radiation and also as the main point of difference between the various investigators in this field.

The very wording of the hypothesis has given rise to contentions as to its proper meaning, the term stimulus especially being the cause of controversial discussion. Holzknacht and Pordes consider that the word itself is ambiguous and vague and that it is used in a different sense from that embraced in the expression "stimulative effect." According to Dejardins, stimulation in the physiological sense occurs whenever any reaction takes place between two bodies and is capable of producing a positive or negative response. Stimulation, then, does not necessarily mean that the reaction must be a positive one: it may be constructive or destructive, but the generally accepted meaning in the literature is that of a positive, constructive effect.

If by stimulation is implied an increase in cellular growth or activity, whether permanent or transitory, x-ray stimulation may theoretically act in one of three ways: (1) It may directly cause an intracellular change in the functioning cells resulting in an increased function or growth; (2) it may indirectly stimulate by causing degeneration of the surrounding cells and removing their inhibiting influence; (3) degeneration of the latter cells may liberate chemical substances which stimulate the functional cells to increased activity.

These diametrically opposed interpretations have resulted in the formation of two main schools of investigators, both conceding that functional activity may follow small dose radiation but differing radically in the conception of the biological processes involved. Manfred Fraenkel

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The current policy of this Journal is not to publish general articles. This paper constitutes an exception in that it was begun at the Editor's request before the policy of restriction was adopted.—Editor.

heads the group which claims that small doses actually stimulate by direct biopositive action of the rays. Holzknecht and Pordes are the protagonists of those who absolutely deny the possibility of any stimulating effect without simultaneous destruction. X-rays always destroy, the degree of destruction being in direct ratio to the amount of radiation. Their interpretation of the increased cellular activity resulting from small doses is not that of a direct stimulative action but that of a depressing factor which frees the cells from a restraining influence.

No attempt will be made in this presentation to review the thousands of experiments which have been performed in an endeavor to correlate the effects of cellular radiation with the Arndt-Schultz law. These investigations have been carried out on unicellular organisms, plants, seeds, vegetations, micro-organisms and on members of the animal kingdom. It has been demonstrated by numerous observers that under certain conditions the tenets of this law are valid. Some of the biological effects which have been observed as a result of weak irradiations may now be discussed.

Acceleration in growth of germinating seeds may be induced (Koernicke and Gager). Radiated buds may show an increase in growth (Molisch). In radiated root tips the number of mitoses may be increased. Bohn effected the first stage of parthenogenetic development through radiation. The rest period of winter buds may be shortened through radiation (Weber). Radiation of sugar cane may not only bring about acceleration of growth but also produce an increase in sugar content. Richards and Packard have accelerated the first stages of segmentation of ova. Lazarus-Barlow and Bektoen experimented with ova of *Ascaris megalocephala* and found that small doses of radiation produced increased cellular division and that heavier doses or more prolonged radiation diminished the rate of division. Gutzeit, Brinkmann and Katschau also were able to demonstrate stimulation by small dose radiation on micro-organisms. Marcus obtained an increase in multiplication of paramecia in cultures. Gillman as well as Baetjer and Congdon noted increased development of eggs in amphibia and birds which was followed by retardation and malformation. Hoffmann observed that radiation in small doses both accelerated and advanced the development of tadpoles. Weak radiation may stimulate the growth of newly born mice and may hasten opening of the eyes (P. Lazarus). Suguira and Failla also noted an increased rapidity of growth in mice with small dose radiation and injurious effects with larger amounts.

Halbertstaedter and Simons conclude from their experiments on horse beans that small doses of x-rays stimulate living tissue and that the stimulating period is preceded by a latent stage which is inversely proportionate in duration to the ray sensitiveness of the cell and the strength of the radiation. This inert interval is considered by some to be due to transitory injurious effect on a particularly sensitive cytoplasm which is followed by an increased compensatory growth (Hirsch). Increased metabolic processes have been observed by several investigators. Redfield and Bright found that low intensities of radiation stimulated cells and tissues

to increased metabolism as evidenced by greater production of carbon dioxide. Barreto, on exposing canaries to small doses, obtained an increased rate of oxygen consumption. Leo Loeb noted an increase in metabolism following small dose radiation.

Numerous investigators have failed to obtain these so-called stimulative effects following irradiation in small dosage. Schwarz, Czepa and Schindler did not succeed in obtaining a constant growth promotion in their thousands of experiments on plants (oats, wheat, beans) but on the contrary observed such variability of results that their original belief in the stimulative effect was changed. They concluded that the so-called stimulative effects of weak intensities of radiation could be explained on the basis of fluctuations in temperature and moisture.

That positive results are transitory and cannot be maintained beyond narrow limits is the contention of Dejardins based upon the experiments of Arntzen and Krebs upon germinating peas. These latter investigators observed that growth promotion was limited to the initial 24 to 48 hours after irradiations, diminishing steadily thereafter.

Frik and Kruger found that the roentgen rays which definitely injured the reproductive capacity of *Bacillus prodigiosus* were not capable of increasing this capacity in doses down to 1/3500 of the injury dose.

In 1923, Ivy, McCarthy and Orndorff presented evidence showing that the submaxillary and gastric glands are not stimulated by small doses of radiation. Orndorff, Farrell and Ivy later noted that 1/10 H.E.D. radiation over the pancreas increased the concentration of lipase and trypsin but did not affect the quantity of the secretion. This group of investigators do not accept the Arndt-Schultz phenomenon as applicable to the action of x-rays on glandular activity.

The experiments with poisons performed by Schnltz and upon which the Arndt-Schultz law was confirmed have been repeated by others who have failed to obtain, however, confirmatory results. Zeller, Heubner, Joachimoglu and Meier all report negative findings.

Pordes reviewed the pharmacological literature on the applicability of this law in that field and reports that there is no Arndt-Schultz law to the pharmacologist. He claims that many medicinal remedies always paralyze and includes in this class strychnine, curare and cocaine, denying a stimulative effect in the smallest dose.

Because of the fundamental differences in conditions resident in the unicellular organism and in the human body, it is felt by many that the entire concept of growth promotion in plants is not equivalent to that obtaining in the complex human body. The value of experimental investigations in the laboratory is minimized when an attempt is made to apply the results to man (Colwell and Rnss, Ewing, Hirsch, Dejardins).

These introductory remarks on small dose radiation outside of the human body have been included for purposes of orientation. In general, one may accept for the purpose of this paper Kotschan's dictum that the Arndt-Schultz phenomenon depends upon the following conditions:

(1) the dose; (2) the effective agent used; (3) the object upon which the experiment is performed; (4) the irritability of the organ in reference to the effective agent; (5) the medium in which the organ or organs are contained; (6) the functional state of the organ at the moment of conducting the experiments. The applicability of these conditions to radiation therapy will be noted in the effects of the x-rays on cellular protoplasm in general and on the endocrine glands in particular.

Cellular protoplasm is susceptible to radiation but the various cells differ in their susceptibility. According to the law of Bergonie and Tribondeau, the more embryonal or undifferentiated the type of cell, the greater is its radio-sensitivity, and conversely the more differentiated and highly specialized the cell, the greater is its resistance.

Cells in mitosis and which are growing are more reactive than those in a resting state. Those containing large amounts of chromatin are more easily acted upon. The endothelial lining of blood vessels is extremely sensitive to both radium and roentgen rays, so that cells having a richer blood supply react more readily than those with a scantier one. The cells of some tissues are affected much more by a given dose of irradiation than are those of another. According to Wolf, the radio-sensitivity of the endocrine glands in the order of their susceptibility is as follows: Adrenal, thyroid, ovary, pituitary, testes, parathyroid.

There is no absolute measure for cellular sensitivity. Normal radio-sensitivity of both tissue and skin is fairly constant and is utilized in determining the dosage of radiation, but that of pathological tissue is so variable and is dependent upon so many factors that it cannot be brought into relationship to skin reactions.

The unit of dosage utilizes the reaction of the skin to a certain quantity of radiation administered. Holzknecht in 1902 advanced the precept that when a definite dose of x-rays is administered to a healthy skin there ensues a definite latent period followed by a definite stage of reaction which commences gradually, rises to maximum and then subsides. The larger the dose, the shorter the latent period, the greater the reaction and its duration. Numerous units of dosage have since been advocated but they all are arbitrary and give a varying degree of clinical value. The term H.E.D. signifies *Hauteinheitsdose* and is sometimes designated as S.E.D., skin erythema dose. It is unfortunate that the doses mentioned in the literature are not standardized, as this interferes with a proper evaluation of the results for purposes of comparison.

The terms small, moderate or large doses are also arbitrary and their use in some instances makes comparison almost impossible. There does not seem to be any definite idea as to just what is meant by a small dose, especially when used in connection with a so-called stimulative effect. To illustrate the difference of opinion and the added difficulty involved in evaluating results, Hirsch advocates the following arbitrary scale of doses: Destructive dose, 100 per cent; inhibitive dose, 75 per cent; stimulating dose, 25 to 35 per cent. In contradistinction to this, the majority of work-

ers in this field consider a stimulative dose to be between 5 and 10 per cent H.E.D. with 20 per cent perhaps as the upper limit. A skin erythema dose should not be confused with a castration dose. It is outside the province of this review to consider in detail the various units of dosage or the action of various wave lengths of radiation.

In his first publication Schultz claimed that a weakened organ is more susceptible to the action of drugs than a normal one. This has been extended by those who accept his law to include the effects of radiation. Fraenkel in various laboratory and clinical studies claims to have demonstrated that tissues and organs which in a physiological state cannot be influenced by x-rays, become more sensitive when they are in a pathological condition. This claim is denied by Dejardins and others.

The necessary requisite for radiation therapy directed against any endocrine gland is primarily a knowledge of the underlying existing disease, but unfortunately this is not always possible at the present time with endocrine disorders. This uncertainty has resulted in the use of the term dysfunction instead of the designation of either hyper- or hypo-function, as the case may be. At best, therefore, any present endocrine treatment must be empirical. The glands which have been irradiated for therapeutic purposes and the indications are: ovary, for the regulation of the menstrual cycle in amenorrhea, dysmenorrhea, oligomenorrhea, and for the cure of sterility; pancreas, to alleviate diabetes mellitus; adrenal, to increase functional activity in Addison's disease and other states of hypoadrenalism; pituitary, to correct certain gynecological conditions, to stimulate the gland in dystrophia adiposo-genitalis and to cure impaired hearing; thymus, for its indirect effect on psoriasis; thyroid, for mental improvement in children, and for direct effect on certain skin conditions.

The pioneer in small dose radiation was Leopold Freund of Vienna, who administered it for conditions of the skin and hair. According to Holzknecht, his interpretations of the effect were erroneous since he based them upon an electrical foundation, but his observations of increased functional activity were correct.

Stimulative endocrine radiation was introduced in 1913 by Manfred Fraenkel, who found that by applying a fraction of the dose required to abolish ovarian function, he was able to induce regulation of the menstrual cycle in amenorrhea and hypomenorrhea. His method, the so-called "Reizbestrahlungen," has since been made use of by numerous gynecologists and roentgenologists and is today one of the accepted procedures in the treatment of certain gynecological conditions.

#### OVARY

The results of small dose radiations in gynecological conditions are open to the interpretations of cellular stimulation in general. If normal regular menstruation and fertility are evidences of physiological ovarian function, then any aberration from the normal may be accepted as symptoms of an impaired function, with certain reservations which will be cov-



ered later in the paper. Fraenkel and his school claim that the beneficial results of ovarian radiation are due directly to stimulation and are evidenced in a local hyperemia of the ovary, an increased cellular nutrition and an increased functional activity. Some, like Thaler, also include a general hyperemia of the entire female generative system and of the intestinal lymphatics among the end results of weak irradiation. Others attribute a biphasic function to the ovary: the production of ova and the hormonal function, each residing in a different set of cells with an individual radio-sensitiveness. Steinach claims that the dose of x-rays which will destroy the follicular apparatus causing amenorrhea will stimulate the so-called interstitial cells or female puberty gland.

Holzknéeht and Borak, on the other hand, contend that radiation in small doses produces a disintegration of ova and of those follicles which are in a diseased or weakened condition, while the healthy functioning cells remain. Due to loss of the disturbing element, the result is one of increased functional activity.

Menstrual disorders are either essential, where the etiological factor resides in the generative system, or symptomatic where the underlying cause is to be sought in constitutional disease. In the latter type, ovarian radiation is of course only a palliative measure. In some instances ovarian radiation is contraindicated, Hirsch including among these tuberculosis, syphilis, pernicious anemia, nephritis, adnexal disease, cystic ovarian tumors and genital tumor.

In polymenorrhea, where the cause lies in follicular changes and in ovarian hypofunction, the results have been fair, according to Seitz and Wieloch, while Wolf has been able to obtain an increase in menstrual flow in some cases. In the absence of other etiological factors, endocrine imbalance is to be considered in dysmenorrhea and radiation attempted, even though the results may not always be successful.

The best results have been obtained in treatment of amenorrhea. Seitz distinguishes between primary amenorrhea, where menstruation has never appeared, and secondary, where it has ceased after having been present. Unfortunately a proper evaluation of the merits of radiation in each type is unobtainable, as the majority of authors do not designate the type present in their patients. According to Seitz, the poorest results are those in the treatment of primary amenorrhea. This author has collected from the literature 239 cases of amenorrhea which were treated by small dosage radiation of the ovaries. Measuring the effects of treatment by return to normal menstrual cycle, his analysis shows that 118 (about 50 per cent) were cured, 14 improved, and 28 failed to react. Pregnancy subsequently occurred in 30 (13 per cent). On the basis of these results, he concludes that there must exist a relationship between radiation, regulation of menstruation and the subsequent pregnancy.

Seitz's statistics cover the reports of Thaler, Flatau, Sippel, Von Rooy, Cauffman, Gal, Heimann, Wagner and Schonhof, Wieloch and himself.

Thaler reported good results in functional diseases of the ovary, based upon the treatment of 147 women, 62 of whom were included in Seitz's analysis. The effects were noted in a few weeks after the institution of treatment. He feels that a patient who does not show any improvement after two or three exposures should not obtain any further treatment.

Flatau in several communications reports success with this type of treatment in women who had failed to improve with previous organotherapy. In 21 cases of sterility, due to hypoplastic or asthenic anomaly of the ovaries, pregnancy subsequently occurred in 12, eight of these being carried to term. He feels that radiation in small doses is an efficient type of therapy in ovarian infantilism, and advises that the field of radiation should include the entire ligamentous apparatus with its nerves and vessels, as well as the uterus and ovaries.

Wieloch believes that the less capable an ovary is of functioning properly, the more difficult it is to effect a favorable result and the smaller dose required to paralyze its function.

Heimann in a later report states that he obtained good results in two-thirds of his cases, two of the women conceiving in 3 to 4 months subsequent to treatment and being delivered of normal, healthy infants. He does not mention the number of cases under observation nor the dosage administered.

Recasens noted that the treatment of dysmenorrhea by radiation in virgins was not as satisfactory as in married women, due in some instances to insufficient development of the anterior uterine wall, which produced an anterior flexion and dysmenorrhea. He used a 20 per cent erythema dose, but he does not mention the number of cases under observation or the percentage of cures.

Drips and Ford, from study of the literature, conclude that there is enough clinical evidence showing favorable regulation of menstruation and subsequent full term delivery of normal infants in women who were formerly sterile to justify its use in carefully selected cases.

In 36 patients with ovarian dysfunction treated by Hirsch, 22 improved, while 14 failed to show any benefit; conception ensued in 7. He administered doses ranging from  $1/10$  to  $1/20$  H.E.D., or 15 per cent castration dose, with slight variations, depending upon the age of the patient, the duration of the condition, and the thickness of the abdominal wall. In reviewing his failures, he found that they were due to the following conditions: Congenital maldevelopment of the entire genital tract, pelvic inflammation, sterility and sexual frigidity, beginning fibrosis of the uterus, with probably a like condition of the ovaries and age, two of the patients being above 36 years old. He refers to Linzenmeier, who observed pregnancy occurring after ovarian radiation in a woman who had a fibroid tumor of the uterus. Thaler is also of the opinion that age of the patient is a factor in the outcome of ovarian treatment by x-rays.

There are others, too numerous to mention, who have obtained good clinical results by irradiation of the ovaries in gynecological disorders. Some radiate the ovaries only, while others include the entire lower abdomen and pelvis.

Experimental studies on animals have been undertaken to determine the type of changes produced by small dose irradiation. Geller, on radiating young rats and rabbits, found no alteration in the cells with 5 per cent erythema dose, but with 10 and 20 per cent H.E.D. there were evidences of degeneration noted in both ova and follicles in all stages without manifestations or predilection for ripe follicles.

His results are not considered applicable to the situation in women, as he studied young animals who had not yet attained puberty. Podljaschuk repeated the experiments but used both young and mature rabbits, i. e., those which had ripe follicles. He found that doses of 25 to 45 per cent H.E.D. did not show any stimulative changes.

Wagner and Schonhof feel that the results obtained in the experiments of Geller cannot be carried over to the mature woman. They selected young women who were to undergo panhysterectomy because of carcinoma of the cervix and applied to one ovary 5 to 10 per cent H.E.D., while the other ovary was carefully protected. At operation, which was performed in two weeks, specimens of both ovaries were obtained and studied. The histological picture in the irradiated ovary was comparable to that in the control, no alterations having occurred that could be construed as evidence of degenerative effect.

Wieloch did not obtain any effect in radiation of the sex glands, while Hooker found that in rats the result of gonad radiation was that of stimulation with small doses and sterilization with large doses. Boruttau exposed young animals to x-rays and obtained stimulation as shown by hypertrophy of the graffian follicles, uterus and mammae.

The possibilities of germinal injury through weak irradiation of the ovaries has been exhaustively studied under varying conditions and with conflicting interpretation of results.

One of the most comprehensive papers on this phase of the subject is that of Nurnberger. He recognizes two types of germinal injury: the phenotype, in which there is some anomaly present in the fetus, and the genetic type, in which the immediate product of conception is normally developed but there is a genetic injury which is manifested only in succeeding generations. The time of conception in relation to that of irradiation is of significant importance in the production of germ injuries and permits a division into two groups: 1. Conception was already present in the ovum at the time of irradiation (Fruition in Stadium der Schädigung). 2. Conception takes place at some time subsequent to the irradiation (Fruition in Stadium der Restitution).

Nurnberger was able to collect 200 instances of pregnancy occurring subsequently to ovarian radiation. Of this number, 4 resulted in the birth

of infants with congenital anomalies. Since this proportion is within the normal limits, according to Nurnberger, he considers that the phenotype injury is an improbable result of irradiation of the ovary. He furthermore contends that if an irradiated mother gives birth to a child with congenital anomalies, the probabilities are that she would have given birth to this type of child even if she were not radiated. Nurnberger's figure of above 3 per cent for the normal incidence of congenital anomalies is higher than that accepted by others, as for instance, Plettrichs, who places it at approximately one per cent.

Bagg and Little were able to demonstrate that mice born of irradiated males and females were themselves apparently normal, but succeeding inbred generations displayed congenital anomalies. The results of their experiments are not accepted as conclusive by Nurnberger, who feels that because of the inbreeding the anomalies were probably recessive in nature and not traceable to the original irradiation. There also seemed to be a selective action as the maldevelopment occurred only in the descendants of one pair. He himself observed no anomalies in 114 animals in the second and third generations of irradiated progenitors. He contends that genetic germinal injury is so seldom seen as to make it of negligible practical significance in radiation therapy of women.

Drips and Ford duplicated the experimental studies of Nurnberger and succeeded in obtaining rats of the second and third generations without the occurrence of a single anomaly. They concur with him that pertinent evidence indicating germinal injury has not been substantiated in the range of low dose radiation, i. e., 5 to 10 per cent erythema dose.

Martius, Hofbauer, Holzkecht and Driesen represent a large group who contend that one must keep in mind the danger of both types of germinal injury in every radiation of the ovaries in women during the reproductive period.

Flaskamp has noted a tendency to abortion in the first pregnancy immediately following radiation, but succeeding pregnancies tend to be normal. He did not observe any anomalies in the aborted fetuses.

Holzkecht objects to radiation of the ovaries in young women on the ground of possible injury to the quiescent as well as the mature follicle.

Douay, however, feels that it is not fair to ascribe eventual sterility to this treatment. The application of roentgen rays in young girls with intractable menorrhagia is the last resort in some instances before hysterectomy.

#### HYPOPHYSIS

Radiation of the hypophysis in small dosage has been advocated in a number of conditions varying in etiology from those in which there is a more or less definite pituitary dysfunction to others in which no such relationship could possibly exist. The most promising field for its application seems to be that of gynecological disorders.

Indications for weak irradiation of this gland are: amenorrhea, especially in women who have failed to obtain relief with ovarian radiation, dysmenorrhea, sterility and in untoward symptoms of the climacteric period. Failure has been noted by Hofbauer in infantilism, in amenorrhea which has lasted more than 3 years, and in menstrual aberration in women above the age of 40 years.

Werner reported that in 13 patients treated by small dose radiation of the hypophysis for amenorrhea, improvement was noted in 7 within a few days or few weeks. He also obtained good results in the treatment in 16 women with dysmenorrhea due to various causes. Successful outcome in amenorrhea and dysmenorrhea by means of weak irradiation of the pituitary was reported by Fraenkel, Hofbauer, Borak, Sahler and others.

Hypophyseal irradiation in conjunction with either ovarian or thyroid radiation has been administered in instances in which pituitary treatment alone was of no avail, or it was felt that because of the symptomatology a dysfunction of the other glands existed. In several cases of associated pituitary obesity and amenorrhea, simultaneous radiation of the pituitary and ovaries was utilized by Reesens in 20 per cent H.E.D. doses with fair results as measured by the disappearance of the menstrual disorder. Seitz, in a similar condition, obtained a cure of the amenorrhea and a subsequent pregnancy which culminated in the birth of a normal infant. Drips and Ford applied radiation in doses of 5 to 10 per cent H.E.D. over the pituitary in addition to that over either the splenic or ovarian regions, in cases of metrorrhagia and menorrhagia, and obtained a temporary regulating effect.

Hallebrand noted a transient relief of epileptic seizures during the course of treatment for amenorrhea by means of 25 to 50 per cent H.E.D. radiation over the hypophyseal region. This result tends to confirm Tucker's observation of some evidence of pituitary dysfunction in 63 out of 200 epileptics and in whom treatment with pituitary extracts seemed to produce improvement.

Hofbauer was the first to attempt massive radiation of the pituitary region, in 1922, for climacteric bleeding and uterine myoma, with apparently good results, but the following year he himself refuted his early claims. Since then negative results have been reported by Hirsch, Werner and Reifferscheid. Hofbauer states that the possibility of cerebral injury with light irradiation is not important, as he has found the brain to be resistant even to massive doses.

The untoward symptoms of both physiological and artificial climacteric, such as headache, mental depression, dizziness, flushes, etc., have been found to be amenable to weak intensities of x-rays. Radiation therapy has been directed at the pituitary, the thyroid and the ovaries.

The menopause syndrome is considered by some to be the result of sympathetic stimulation, due to hyperactivity of the hypophysis and

thyroid in the absence of the antagonistic ovarian hormone (Adler, Munk, Schikkele, Mayer, Borak). Borak advises radiation in doses from 5 to 30 per cent H.E.D. of the thyroid and hypophysis in these conditions. He obtained amelioration of symptoms in 35 instances out of 47 patients treated by this method. According to him, hypophyseal radiation should be instituted prior to that of the thyroid in those instances in which the climacteric syndrome is accompanied by an increase in weight, but it should follow thyroid radiation if the symptom complex is attended by a loss of weight. If improvement is not noted within a few days after the institution of treatment, the radiation should be repeated in 8 days. Occasionally a recurrence of symptoms is noted later.

Porehownik reports his observations on 16 women who were treated for climacteric symptoms, 2 of them being of the artificial type, following intense ovarian radiation. He administered  $1/6$  to  $1/10$  H.E.D. over the hypophysis, repeating in 3 to 4 weeks if necessary, i. e., if no improvement was noted within ten days after the treatment was begun. Thyroid radiation in  $1/3$  erythema dose was then resorted to in the event of a failure after the second series. He states that this method of treatment invariably gave good results, evidenced by a drop in blood pressure in addition to general improvement.

This effect on high blood pressure was also noted by Groedel in both artificial and natural menopause by small dose radiation of the ovaries. Werner reported improvement with small dosage of x-ray over the pituitary and mid-brain regions. Seitz quotes M. Fraenkel to the effect that the latter noted excellent results in two women, 34 and 38 years of age, respectively, who had roentgenological climacteric. Small dosage radiation over both the ovarian and thyroid regions was followed by the return of a regular menstrual cycle and subsequent pregnancy in both women within six months. Seitz states that the results are variable, as he has observed both success and failure with 10 per cent H.E.D. in the same type of a case.

Benjamin agrees with Fraenkel and Leschke's opinion that mild radiation of the thyroid, pituitary and adrenal glands, in addition to the ovaries, will play an important part in so-called "rejuvenation."

In analyzing the radiation treatment of the climacteric, one is left with a feeling of uncertainty and confusion. Some authors administered large or middle size doses to the pituitary or thyroid, others utilized small radiation on these glands, while still others used so-called small doses on the thyroid, pituitary and thyroid. The difference in opinion as to the effects of radiation is never so marked as in the treatment of this particular syndrome.

If the symptom complex of the climacteric is due to hyperactivity of the thyroid and pituitary glands and hypofunction of the ovary, then it is difficult to consider improvement from the viewpoint of stimulation of all the glands involved. It would be more reasonable to expect the treat-

ment to consist of measures tending toward a depression in the activity of the thyroid and hypophysis by massive doses and a stimulation of the ovaries by small doses. It is fallacious to conceive of stimulation in all three glands by small dose radiation. If simultaneous or individual treatment of the hypophysis or thyroid in small dosage brings about an improvement in this supposedly hyperactive syndrome, then small doses in this instance are not stimulative.

In 1922 Stokes advanced a method of small dose radiation of the hypophysis for the amelioration and cure of impaired hearing. The dosage he advised was below  $1/50$  erythema dose, one well under the stimulative line. According to him, the ultimate result that he hoped for was not that of stimulation, but an equilibration by a restoration of the acid-base balance in cell protoplasm. The best results were obtained by a series of 10 to 20 treatments at short intervals, daily if possible. The method was soon taken up by others, notably McCoy, Jarvis, Richardson, Orloff and Siebenman.

While Stokes states that there can be no doubt of these diminutive doses penetrating the skull and reaching the pituitary gland, other workers in this field are not so ready to attribute the beneficial results noted by them to any action on the gland.

Richardson obtained improvement in 60 per cent of his patients in his series of 600 cases of aural disturbances, regardless of their original etiology. He feels that the therapeutic effects might not depend exclusively upon stimulation of the pituitary or the auditory nerve center, but that possibly the nerve itself and associated non-neural tissue might be subject to the action of the rays. He argues that while it is true that microscopic examination reveals very slight, if any, alteration in nerve and brain tissue following x-ray exposure, still it is possible that radiation will affect nerve structures chemo-electrically.

In McCoy's series of 45 patients suffering from various types of deafness, 30 per cent were greatly improved, 50 per cent somewhat improved, and 20 per cent not improved by small dose pituitary radiation. Among the subjects were 6 of otosclerosis, two of whom were greatly improved by treatment. He considers that the method is still empirical, is not harmful but in many instances is beneficial. He theorizes that there must be an absorption of small cell infiltration in the Eustachian tube, and possibly at the termination of the auditory nerve as well as perhaps stimulation of the auditory nerve. The status of possible pituitary stimulation he is unable to place, but he feels that there may be some basis for it on the ground of alteration in blood pressure attending treatment.

Jarvis came upon this method during the course of treatment radiation of hypertrophy of the lingual tonsil, when it was noted that a difficulty in hearing which had been present for ten years had cleared up. On extending the method to other instances of impaired hearing, he found that improvement ensued especially in those patients whose throat symptoms

were part of a general picture of lymphoid hyperplasia. He concludes that the results are due to the beneficial action of radiation upon lymphoid tissue, and to some extent upon the germicidal effect of the rays.

Tousey found that in pituitary radiation for chronic otitis media, the hearing improved after the aural discharge and pain had ceased. He attributes the improvement to pituitary stimulation.

In attempting to find a biological basis for the x-ray treatment of impaired hearing, Pacini photographed the changes produced in the brain and nerve structures produced by small dose radiation. He considers that the alterations indicate that the rays affect the associated cortical centers and the transmissibility.

An endocrine basis for otosclerosis is advanced by Drury, who found after exhaustive scientific studies that there was a distinct endocrine glandular dysfunction in 50 per cent of his patients. He noted a marked improvement in the ear condition upon the exhibition of the appropriate organotherapy. Although the relationship is not entirely clear, he is of the opinion that the pituitary, thyroid gland and ovary are implicated.

It will be noted from this brief review of the literature on pituitary radiation treatment for impaired hearing that the consensus of opinion, even among those who find this method successful, is contrary to Stokes' contention of pituitary stimulation.

Carlson emphatically denies the possibility of pituitary stimulation in the treatment of impaired hearing. He considers the relationship in general between the endocrine system and upper respiratory disorder, and concludes that such a relationship does not exist. When associated with acromegaly, tinnitus and deafness is generally due to an increased intracranial pressure. Stimulation of any nerve organ by way of the pituitary is not tenable, as this gland does not govern directly nor indirectly the metabolism of the brain or its receptors. He considers it ridiculous to suppose that indiscriminate radiation of the head in the general direction of the pituitary is capable of producing regeneration and restoration of the acid-base equilibrium in the cells of the gland and thus bring about a return of hearing.

Evidence of parathyroid dysfunction as cause of disorders in the tract under discussion is as yet extremely doubtful. The sneezing and irritation of the nasal mucous membrane in dogs ascribed to parathyroid deficiency, he thinks, are due to vascular changes in the mucous membrane secondary to disturbances in the irritability of motor and sensory nerves. The gonads, adrenal and pancreas are eliminated in a consideration of possible etiological factors in the production of diseases of the ear, nose and throat. The only gland, according to Carlson, which calls for a thorough investigation from the point of view of possible relation to the infectious disease of this system, is the thyroid.

Hypophyseal radiation has been utilized in the treatment of dystrophia adiposo-genitalis. Variable results have been obtained in this condition



when associated with amenorrhea or other gynecological disorders. Treatment in children by small dose radiation has also met with inconstant results.

Ascoli and Fagioli obtained remarkable improvement in a case of Froelich's syndrome associated with asthma in a boy 15 years of age. Pituitary radiation was tried after he had been on pituitary extract and other organotherapy for a long period of time. The treatment consisted of weak irradiations one month apart for four months. Twenty-five days after the initial visit there was an increased activity in both primary and secondary sex characteristics as evidenced by an increase in pubic hair, increase in the size of the penis, increase in height, decrease in fat, appearance of erections, which became more frequent and complete, and the accentuation of sexual appetite.

Similar results are reported by Wieser of Vienna in several instances of this disease. Carlson considers these cures as modern miracles, and states that "Evidently we are witnessing the beginning of a race between the roentgenologists and surgeons as harbingers of virilism."

Ascoli and Fagioli were unsuccessful in the treatment of eunuchoidism in a man of 26 years of age in whom they radiated by small doses the pituitary, thymus and testes.

Wintz feels that hypopituitarism even in its extreme degree, as exemplified in Simmons' disease, is not to be treated by weak irradiation of the gland.

Detailed reference will not be made to the numerous experiments which have been performed in the laboratory on the effects of weak hypophyseal irradiation.

Suffice it to say that the results are not conclusive, some obtaining an increase in growth, while others noted a diminution in addition to the production of genital hypoplasia. To complicate the subject still further, Poos claims that whenever any organ is exposed to the action of the x-rays, a pathological change takes place in all radio-sensitive organs. He obtained the same result on raying the legs of animals as on radiating the hypophysis.

In any consideration of the effects of radiation of the pituitary, one must take cognizance of the anatomical and functional relationship existing in this region of the mid-brain. Here are controlled metabolic processes, water exchange, heat regulation, sexual development and certain endocrine functions. Localized radiation must necessarily act on both the hypophysis itself and on the vegetative centers in its vicinity; how much of the functional activity attributed to the gland is performed by the surrounding structures is still a mooted point.

#### ADRENAL

In any evaluation of the effects of irradiation on the adrenal, consideration must be given to the variable radio-sensitivity of this gland

According to Holfelder and Peiper, this varies to such an extent that it is exceedingly difficult to state in advance the effect of any given dose, thereby explaining the contradictory results obtained with the same dose in different individuals. The adrenals are twice as sensitive as the intestinal epithelium and should therefore be excluded from the field of exposure in the treatment of other organs in their vicinity.

These limitations upon adrenal radiation therapy must be kept in mind in evaluating the reports in the literature.

David and Hirsch studied the action of radiation upon the adrenalin and blood sugar content in guinea pigs, dogs and rabbits, one adrenal being exposed while the other was protected. They found that distinct functional increase resulted from a 25 per cent H.E.D., as evidenced by an increase both in the blood sugar level and adrenalin content. Larger doses, one H.E.D., produced a distinct diminution in function. Their observations have been confirmed by Hesse.

Golobinin reports his findings in a case of Addison's disease in a man 27 years of age. Long continued organotherapy was without effect, but after small dose irradiation of the adrenal region improvement set in, as evidenced by an amelioration of the general condition, increase in weight and disappearance of the cutaneous pigmentation. The treatment consisted of small doses (strength not stated) for 50 sittings over a period of 70 days. Wiesner also obtained improvement with a similar method of long continued treatment.

Holfelder and Peiper protest against what they term these blind methods of treatment without first knowing or determining the radio-sensitivity of the adrenal glands of that particular patient. There are several reports of injury to the adrenals following radiation, such as that of Harvey, who found evidences of bleeding in the adrenals and degenerative changes in the zona glomerulosa. Descastellos and Zimmern and Cottenot observed adrenal injury, the latter, however, after larger doses (3 to 6 H.E.D.).

Levy-Dorn and Weinstein obtained a transient slight rise in blood pressure following small dosage, but they were unable to determine any definite relationship between the intensity of the reaction and the strength of the dose. Results such as these are not accepted by other investigators, as, for instance, Holfelder and Peiper, who conclude on an experimental basis that the possibility of diminishing functional activity of the adrenal cortex by irradiation is plausible, but the medulla does not seem to be influenced by x-rays. The reduction of adrenal function in terms of blood pressure is at least problematical. The idea of a stimulating dose must remain for some time a Utopian one.

There are numerous reports in the literature on the effect of irradiation of the adrenals in so-called small doses in diabetes mellitus (Stephan, Dresel, Zimmern, Cottenot and Benmer). On study of the reports, it is found that the exact strength of the dose is not mentioned or else it was

above a 25 per cent erythema dose, and therefore cannot be accepted as being an instance of small dose radiation. Practically all of the reports show a diminution in glycemia and an improvement in diabetes mellitus, surely not an example of stimulation, if it be conceded that the adrenal gland is hyperactive functionally in this disease. These results should be construed as tending to show that radiation of the adrenals in doses larger than 25 per cent H.E.D. may produce temporary recession of diabetes mellitus by a diminution in adrenal activity.

#### THYROID

In contradistinction to the vast amount of literature on the x-ray treatment of exophthalmic goitre and hyperthyroidism, there is a paucity of information on the effects of weak irradiation of the gland in hypothyroidism, in spite of the fairly frequent occurrence of the latter condition.

Stimulation of metabolism as evidenced by an increased basal rate and hyper-excitability of both motor and sensory nerves has been observed by Leo Loeb. Increased functional activity in reference to carbohydrate metabolism has been noted by Brosamen, who found a hyperglycemic curve following small dose radiation and a depressed curve after large amounts of radiation.

McCord and Marinus report some interesting experiments in which they studied the rate of metamorphosis in normal tadpoles, in non-irradiated but thyroid-fed tadpoles, in irradiated only and in those which were irradiated and then subsequently fed thyroid extract. It was noted that irradiation itself is without any apparent effect on normal tadpoles, but that it increases the functional activity of thyroid extract when administered subsequently by an alteration of the susceptibility toward that hormone. This change in the cellular susceptibility or in the production of a subsequent increased hormonal activity was also demonstrated by Fogelberg, who studied the effects of radiation in small doses on the sugar curve in 22 patients; 2 of these were normal, 4 had simple goitre, 3 exophthalmic goitre and 13 thyrotoxicosis. All failed to show any effects after simple, weak thyroid irradiation, but on the subsequent ingestion of 100 grams of glucose presented a typical hyperglycemic curve.

The relationship of certain skin conditions to thyroid hypofunctioning has been stressed lately, especially in eczema and scleroderma. Guarini and Donah report improvement in eczema following the administration of weak irradiation of the thyroid.

Ascoli and Fagioli noted improvement in scleroderma in a woman 56 years of age after irradiation of both the thyroid and pituitary regions. Hammer accepts the basis of a dysfunction of the thyroid in this condition, but claims that the x-rays decrease the functional activity of the gland instead of increasing it. In his two patients, one of whom had a thyrotoxicosis and the other a simple goitre, weak irradiation of the thyroid resulted in a clearing up of the scleroderma.

Thyroid radiation has been utilized in both massive and weak intensities in the treatment of gynecological conditions, but in order to place roentgenotherapy of this gland upon a rational basis in this field, it must first be determined whether one is dealing with an increased or a decreased functional activity of the gland.

According to Wintz, thyroid-ovarian disorders may be grouped under the following classification: (1) Thyrogenous dysfunction of ovary secondary to a hyperthyroidism. (2) Oophorogenous hyperthyroidism, the primary ovarian condition being exemplified in operative removal of the ovary and in disappearance of ovarian function in both physiological and artificial menopause. (3) Ovarian dysfunction upon the basis of hypothyroidism. In this condition, amenorrhea is accompanied by dry skin, edema, water retention and obstipation.

In the treatment of any of these disorders, the underlying cause must be eradicated before a cure can be expected; any other measures are merely palliative. Weak irradiations are, of course, contraindicated in hyperthyroidism of both primary and secondary types. In the third type, that of simultaneous ovarian and thyroid dysfunction, the results of weak irradiation directed against the thyroid are apparently not as effective as against the ovaries. Wintz and others advise that in these conditions irradiation of the ovaries be accompanied by the administration of glandular material. Sehrt, Seitz, Wintz, Recaseus and others have obtained good results in hypothyroid amenorrhea with the use of ovarian and thyroid extracts, but they have noted a recurrence of the amenorrhea attending the discontinuation of thyroid extract.

Wieser reports the results of radiation of 360 patients with various endocrine disorders. As it was not always possible to arrive at a diagnosis upon the basis of the history and clinical findings, he utilized the Abderhalden test and the exchange of gases in addition. Upon the basis of these methods of diagnosis, he radiated the pituitary, thyroid and gonad, administering 2 to 10 per cent H.E.D. over the gland or glands involved every four weeks for about three months. In some instances a second series was necessary, and in others a transient retrogression was observed in about three weeks after the onset of treatment. Organotherapy and other treatment directed against the original etiological factor, such as lues or tuberculosis, was simultaneously given. Only 4 per cent failed to give some response. He includes mongolian idiocy among the conditions which were not amenable to treatment, but he further reports marvelous improvement in two children with this otherwise intractable disease. These patients were 3 and 7 years of age, and after radiation the characteristic earmarks of this condition, such as over-extension of the joints, epicanthus and cutaneous manifestations, were altered to so marked a degree that it was barely possible to recognize the children as mongolian idiots. Other instances of astounding results were obtained in imbecility, dwarfism, dysgenitalism,

chondrodystrophy, homosexuality, behavior disorder, Froelich syndrome and myxedematous idiocy.

#### PARATHYROID

There are no available clinical reports of parathyroid radiation, due to the difficulty in radiating this gland without at the same time affecting the thyroid. Experimental reports of increased calcium content after weak dosage of x-rays directed at this gland must be considered from the same viewpoint.

#### THYMUS

The meager literature on the effects of weak irradiation of the thymus is concerned for the most part with their results noted in the treatment of skin disorders. We find here the same controversial discussion as to the causal relationship of the gland, some, like Brock, Weinhardt and Klingmüller, contending that there is such a connection, while others, like Schneider and Weber, disputing the claim.

Brock has observed improvement with weak irradiation in lichen planus, psoriasis, ichthyosis and varrucosis. Weinhardt and Parker also obtained good results in psoriasis, the latter asserting that a cure can be obtained in 85 per cent of the cases by means of this treatment. Steiger assumes that the thymic dysfunction belief is substantiated by the observation that children with status thymo-lymphaticus rarely have psoriasis.

Schneider has not been able to obtain the results reported by Brock, as he succeeded in only two cases out of 12 in clearing up the condition. Instead of an improvement, Weber observed an aggravation of psoriasis in his patient.

Thymus radiation has been used in exophthalmic goitre. Ascoli and Fagioli noted a recession of the goitre and an improvement in hyperthyroid symptoms in two patients subjected to thymic radiation in small dose.

Most exacting experiments were carried out by Lenz, who studied the alterations produced in the thymus glands of rabbits by varying strengths of radiation. The gauge of stimulation was the increase in the number of mitotic figures as shown by Dustinn in his experiments in mice after intraperitoneal injection of horse serum. Lenz's results may briefly be summed up as follows: A single large dose produces involution of the thymic parenchyma with complete absence of mitotic figures. With moderate doses, regeneration takes place in 11 to 12 days, as shown by the appearance of mitotic figures, and is complete in approximately three weeks. With small doses there is a progressive involution of the parenchyma, but no demonstrable attempt at regeneration. The experiments show that thymic glands which are the seat of either age or accidental involution cannot be stimulated by even as small a dose as 1/40 erythema dose, but on the contrary, normal involution progresses more rapidly. Lenz claims that this rapid destruction of the thymus probably upsets the endocrine balance

of the body and liberates proteins previously kept in combination with the parenchymal cells. Whether clinical improvement occasionally seen after irradiation of the thymus can be explained on this basis or not, stimulation of this organ is not responsible for the change.

Manfred Fraenkel has recently advanced the opinion that certain glands possess the power to combat cancerous growth, and that stimulation of these glands will result in checking its progress. He has advised weak irradiation of the thymus and thyroid in mediastinal tumors and of the pituitary in carcinoma of the eye. This conception is of too recent a date to be discussed here.

The thymus is considered to be involved in epilepsy from the view point of both an increased and diminished functional activity. Strauss believes the condition to be due to endocrine dysfunction and advises radiation in small doses of the adrenals and thymus. Symmers, on the other hand, has noted that epileptic seizures often cease at puberty, at the time when the thymus gland undergoes involution with a resultant diminution in gland activity. On this basis, he advises intense radiation of the thymus in those epileptics especially who show stigmata of status thymolympathicus.

#### PANCREAS

The results obtained in weak irradiation of the pancreas are not sufficiently definite to warrant the expression of any opinion at the present time.

Peterson and Saelhof conclude from their experiments on dogs that in pancreatic deficiency due to partial pancreatectomy, roentgen irradiation of the pancreatic rest produces a transient increase in sugar output, which is followed by an increase in carbohydrate tolerance. The increased tolerance may be transient or may extend over a period of several weeks. The effect on the blood sugar varies; there is usually a temporary increase, to be followed by a lowering of the level within a few hours to several days. The effects are attributed by the authors to direct stimulation of cellular metabolic processes and not to vascular alterations. They feel that the changes in carbohydrate metabolism accompanying various strengths of radiation over the pancreas are in keeping with the Arndt Schulz phenomenon. It is felt that the clinical application of weak irradiation in the management of diabetes mellitus is not to be considered, however, until further knowledge concerning the ultimate effect of x-ray stimulation on pancreatic tissue is obtained. The authors feel that its use in diabetic coma may be warranted when other types of treatment have failed.

Stephen exposed the pancreatic region to stimulating doses of x-rays, and observed in two cases of diabetes mellitus an increased tolerance for carbohydrates and a diminished excretion of sugar.

In evaluating the effects of pancreatic irradiation, it must be remembered that an augmentation in the sugar output may be due to general radiation and stimulation of the abdominal viscera by secondary rays.

## TESTES

There is very little available literature on the effect of weak irradiation on the testes. Wolf claims that they are more radio-resistant than other glands and require from 3 to 5 times as large a dose as the ovaries to obtain approximately the same results.

Benjamin reports the administration of roentgen rays on the testes in supposed hypofunction, but he was unable to obtain any result tending to show any increase in gonad function.

## CONCLUSION

In this paper there has been presented a review of the literature on the so-called stimulative effects of roentgen rays on endocrine glands.

The question at issue is not the presence of an increase in body weight, activity and functional capacity following irradiation in small doses of x-rays, but the determination as to the fundamental underlying cause of this reaction—is it a direct stimulative effect or is it the result of complicated processes not stimulative in nature?

From a clinical view point, weak irradiation does increase functional activity as especially illustrated in the treatment of gynecological disorders by irradiation of the ovaries. The clinical application of pituitary radiation, while beneficial, does not imply always a stimulating action; some of the results are probably due to destructive effects. The results noted in the treatment of childhood endocrinopathies by irradiation of the thyroid, pituitary and gonads are startling at the hands of one particular investigator, but they should be confirmed by others before they can be accepted. Radiation of the adrenals, pancreas, testes and parathyroid has not given us any definite information as yet in the treatment of dysfunction of these glands.

Stimulation by means of roentgen rays may in time be one of the methods of procedure in the treatment of endocrinopathies, but before this is possible it must be placed upon a scientific, accurate and rational basis. A proper knowledge of the underlying endocrine factors in the causation of the disease and a standardized method of radiation with a standardized table of dosage are necessary requisites before any hope can be entertained for success in stimulative radiation.

## SUMMARY

This paper is a review of the literature on the stimulative effects of x-rays on endocrine glands. A biological basis for the stimulative action is found in the Arndt Schulz law, which states that "weak stimuli accelerate vital processes, moderate promote them, strong inhibit them, and strongest destroy them." The increased functional activity noted after radiation is interpreted according to two view points: Fraenkel believes that there is a direct stimulative effect on the cells in accordance with the Arndt Schulz law, while Holzknecht and his school deny any stimulative

action, claiming that x-rays always destroy in no matter what dosage. They contend that increased cellular activity is due to the freeing of a restraining influence of a depressing factor.

Thousands of experiments have been performed on seeds, vegetations, plants and micro-organisms demonstrating that this law is valid and is applicable to the action of x-rays. This is denied by others, who in addition feel that the entire concept of growth promotion in plants and in cellular organisms is not equivalent to that of the complex mechanism obtaining in the human body.

It is difficult to evaluate or compare results in the reported cases because of lack of uniformity in expression of dosage and in standardization of strength. The small dose of one author is a moderate strength of another.

The widest application of small dosage radiation has been in the field of gynecology. There is enough clinical evidence showing favorable results from weak irradiation of the ovary to justify its use in carefully selected cases. Successful outcome has been reported by many authors in more than 50 per cent of their cases of amenorrhea, as evidenced by the return of a normal, regular menstrual cycle and in the occurrence of more than 200 instances of a subsequent pregnancy, with the delivery of a normal infant in all but 2 per cent. While some minimize the dangers, the possibility of germinal injury must be thought of in the ovarian radiation of any woman during the reproductive period. The results in the treatment of dysmenorrhea and oligomenorrhea have been fair. Some authors claim that the ultimate outcome of radiation therapy in gynecological conditions depends upon the age of the patient, the duration of the disorder and the thickness of the abdominal walls.

Untoward symptoms of both physiological and artificial climacteric periods have been treated by irradiation of the pituitary, thyroid and ovaries with amelioration in most instances. Some administered large or middle sized doses to the pituitary or thyroid, others utilized small radiation of these glands, while still others used so-called small doses on all three glands. If the symptom complex is due to hyperactivity of the thyroid and pituitary glands with a hypoactivity of the ovary, then it is difficult to consider improvement from the viewpoint of stimulation of all the glands involved. It is fallacious to conceive of stimulation in all three glands by small dose radiation. If simultaneous or individual treatment of hypophysis or thyroid in weak intensities brings about an improvement in this supposedly hyperactive syndrome, then small doses in this instance are not stimulative.

Pituitary therapy in impaired hearing, as advocated by Stokes, has no scientific basis, and the results are not considered as being due to stimulation of this gland even by the majority of those who have obtained good results following its use.



Treatment of Froelich syndrome has not been uniformly successful with weak irradiations, especially when accompanied by amenorrhea.

The radio-sensitivity of the adrenals is so marked that it is difficult to state in advance what the result will be with any given dose. The effects of weak irradiation of this gland have not been uniform for this reason; some of them have been increase in blood pressure and in the blood sugar level. A few instances of improvement in Addison's disease have been reported.

There is a paucity of information on the utilization of weak radiation of the thyroid in hypothyroid states, in spite of the fairly frequent occurrence of the condition. Increased functional activity, as evidenced by an increase in basal metabolism and sugar metabolism, have been noted in the laboratory. Improvement in eczema and scleroderma and in ovarian dysfunction due to hypothyroidism, has been reported, but in the latter condition benefits are noted only during the time of simultaneous oral administration of thyroid extract.

Startling results are reported by Wieser of Vienna in the treatment of childhood endocrinopathies and related conditions, including mongolian idiocy, by irradiation of the pituitary, thyroid and gonads. Where the diagnosis cannot be made upon the history and clinical picture, the Abderhalden test and gas exchange are utilized.

There are no available reports on the effect of radiation of the parathyroid. It would be difficult to radiate this gland without at the same time striking the thyroid.

Exacting experiments by Lenz force him to the conclusion that there is no evidence of any stimulative effect on the thymus as the result of weak irradiation.

M. Fraenkel has recently advanced the opinion that certain endocrine glands possess anti-cancer influence, and upon this basis advises stimulative irradiation of the thymus and thyroid. This concept is of too recent date to be discussed here.

Improvement has been noted by several in the irradiation of the thymus in certain skin conditions.

There are a number of case reports in the literature on the beneficial effect of small dose radiation in diabetes mellitus, but on analyzing the original papers, it is found that either the exact doses are not mentioned or else a strength above 25 per cent H.E.D. was used—surely not an example of a small dose. The results obtained by small dosage radiation of the pancreas are not sufficiently definite to warrant the expression of any opinion at the present time. Increased carbohydrate tolerance has been reported after weak irradiation, but it is felt that the clinical application of this method of treatment should not be considered in the management of diabetes mellitus until there is further light on this subject.

There is very little available literature on the testes or pineal.

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## THE USE OF CORTIN IN ADDISON'S DISEASE

FRANK A. HARTMAN, A. H. AARON AND J. E. CULP\*

From the Physiology Laboratory of the University of Buffalo and the  
Buffalo General Hospital

BUFFALO

Cases of Addison's disease have been treated by adrenal preparations (Rowntree, 1; Cohoe, 2). Whole gland or whole cortex have been used. Some cases showed definite improvement.

Cortin, a substance obtained from the adrenal cortex, enables adrenalectomized cats and rats to survive indefinitely (3), (4). If Addison's disease is due to a deficiency of cortin, the injection of the latter should ameliorate the condition.

We are reporting the effects of cortin injections in one case. This is warranted because repeated reduction or withdrawal of the substance has demonstrated conclusively that the patient is kept alive by cortin. Not only was the patient revived from an apparently moribund condition but four times the cortin has been reduced or discontinued and each time there has been a decided relapse. Recovery from these relapses occurred when cortin was increased.

The patient, a man 24 years old, had scarlet fever in February, 1928, the illness lasting one month. During the winter of 1929-30 he continued to work but did not feel like going out in the evening as he had previously. He remembered two attacks of gastric upset in this period.

At the time of admission to the hospital he had been very ill for six weeks. Nausea and frequent vomiting made it difficult to retain any but liquid foods. His weight had been reduced about twenty per cent. He showed characteristic pigmentation. The face, neck and forearms, parts which had been exposed to the sun (he had worked outside), appeared to be strongly sun-burned, but in addition there were small "black freckles" plentifully distributed over the body in protected as well as unprotected regions. There was a brown streak on the skin above the spine and brown discoloration on the hips apparently where clothing had pressed against the body. There was also brownish pigmentation of the gums over the two central upper incisors.

When first seen he appeared to be in shock. His pulse was feeble. His blood pressure was 50 mm. systolic, 20 mm. diastolic in both arms. He complained of feeling cold. Blankets and hot water bottles were applied. Every available method was adopted to introduce water into the tissues. At first 1000 cc. of isotonic NaCl solution was introduced by hypodermoclysis. Small amounts of fluid were taken by mouth. Six hours later 1000 cc. of 5 per cent glucose in isotonic NaCl solution were

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injected intravenously and glucose was given by the Murphy drip method. Between four and five liters of fluid was introduced into the tissues during the first twenty-four hours. He was quite drowsy and dozed much of the time. At the end of the 24 hours he was no better; his blood pressure was 58/30. His pulse was very weak and thready. He was extremely restless so that he kept moving his legs, hands and feet. His legs twitched and he complained that they felt numb and tingled. He talked irrationally.

Adrenalin (1 cc.) was injected subcutaneously every two hours but was discontinued by the third day. One liter of 5 per cent glucose in isotonic NaCl solution was given intravenously twice every 24 hours for seven days. Digitalis was given for three days.

Cortical extract was not available until 24 hours after admission. An injection of 5 cc. was then made intravenously. Thirty minutes later 10 cc. was given subcutaneously. Three and one-half hours after the first injection three injections (10 cc. each) were made subcutaneously with forty and seventy minute intervals. Additional extract was not available for four hours, but after that 10 cc. was injected subcutaneously every hour until a total of 150 cc. had been injected in the twenty-four hours. The amounts injected after this are indicated in the chart (1 cc. contained the yield from about 15 gm. of cortex).

Three hours after starting the cortical extract the patient was quieter. At nine hours the pulse was 100 per minute, the temperature 100 and the respiration 26 per minute. He again became irrational and voided urine in bed a number of times. By morning (20 hours after cortical extract was instituted) he was sleeping at long intervals but was very restless when awake. During the next night he was very irritable and hard to manage. His pulse was of fair quality and his blood pressure was 74/32. He improved during the third day, dozing much of the time. He slept most of the third night and seemed much brighter in the morning. He ate his first meal (breakfast) at this time. He read and took an interest in his surroundings. His appetite and general condition continued to improve so that by the fifth day after instituting cortical extract he was eating bread, butter, chicken and potato. He no longer slept much in the daytime, his night's sleep apparently being sufficient. He appeared fresh and rested when observed in the morning. His mental activity also increased. He read much of the time and talked with visitors.

It will be noted in the chart that the amount of cortical extract was gradually reduced until he was receiving only 20 cc. in 24 hours (5 cc. every six hours). Eleven days after cortical extract had been started he refused food at noon and complained of feeling cold that night. The next morning orange juice nauseated him and by eleven A. M. he was very ill. Cortical extract (10 cc.) was given intravenously and two more injections (10 cc. each) within an hour. Extract (10 cc.) was then given subcutaneously every hour for thirty-six hours and then every two hours for a few days as the chart indicates. With this relapse temperature rose, blood



pressure fell, pulse rate increased and the old symptoms returned. He became cold, restless and mentally dull. He slept much but did not appear rested. He was easily nauseated. Fluids were administered as before and glucose injected twice daily for three days. Within two days after increasing the extract the patient showed marked improvement. Blood pressure had risen; the pulse was slow and of fair quality. There was mental alertness instead of restlessness and apathy. Nausea was absent and the patient began to eat. He steadily improved.

In an attempt to find the minimum dosage required, the extract was reduced on the twenty-fifth and thirty-fifth days. A few days after the second reduction the old symptoms appeared, viz., loss of appetite, nausea, vomiting and asthenia. An increase in dosage brought about recovery.

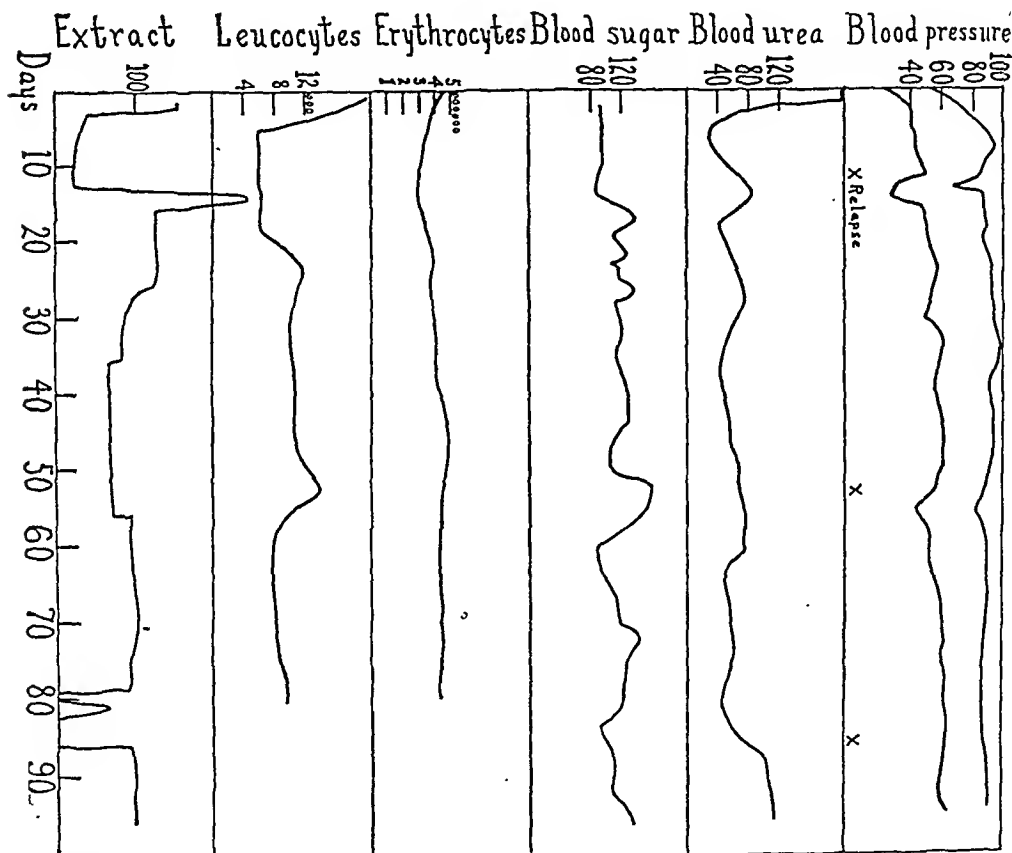


Chart I. Blood changes in a case of Addison's disease beginning with an attack that proved to be fatal. Injection of cortical extract produced recovery. Reduction of extract caused serious relapses (x). Blood urea and blood sugar in mgm. per 100 cc. Extract in cc. (Blood urea should be 130—120 at first.)

Extract was discontinued except for one day for about eight days on the seventy-eighth day. In about three days after discontinuation symptoms reappeared. Injections caused them to disappear. It is difficult to account for these effects except through the action

Changes have been observed which will be discussed.

*Temperature:* The patient has had fever twice; first, for five days after entering the hospital, and second, during the first relapse. At all other times the temperature has been subnormal. During the second relapse the temperature ranged about 97° F. This lasted about two weeks. At other times it ranged about 98° F.

*Pulse:* The pulse rate has ranged from 70 to 90 per minute except during the febrile periods.

*Blood Pressure:* The highest the systolic pressure has been is 100 mm. Both systolic and diastolic pressures have fallen during the relapses, although only to a small extent during the third one (see chart).

*Blood Urea:* The blood urea was very high (130-120 mgm. per 100 cc.) during the first three days after admission, but as the symptoms disappeared it fell rapidly. It gradually rose again as the extract was decreased and again fell with the second remission.

The blood urea has risen with each relapse, but does not keep pace with the condition of the patient. He may be very ill before the urea shows much of a rise. There may also be a lag upon recovery. The urea does not necessarily fall promptly with amelioration of the symptoms.

It has been found in adrenalectomized cats (5) that the blood urea becomes very high in the terminal stages. If the animal recovers the blood urea falls. It has also been shown in animals that a high blood urea can be reduced by the injection of cortin.

Rowntree (1) has shown that the blood urea falls when the patient improves.

*Blood Sugar:* The blood sugar was low (82-86 mgm. per 100 cc.) even during the administration of glucose. It remained low until after the first relapse. It has fluctuated considerably as shown by the chart.

*Blood Cells:* Changes in the number of erythrocytes and leucocytes are shown in the chart. The large count at the beginning is probably accounted for by dehydration. The highest erythrocyte count was obtained 42 days after beginning treatment.

Following each relapse during recovery there has been extensive desquamation of the skin.

*Addendum:* A fourth relapse occurred after the chart was made. Increase of extract produced recovery. It has now been more than five months since treatment was started.

The results in this case indicate that cortin deficiency is an important factor in the causation of Addison's disease.

#### SUMMARY

A subject of Addison's disease with notably dubious prognosis was revived and has been kept alive for more than five months by the injection of extract of the adrenal cortex. Four relapses have occurred following reduction of the extract. A few hours after increasing the extract after a relapse, improvement was evident each time, and in two or three days

recovery was almost complete. The appetite returned and mental activity became normal.

Each relapse was accompanied by a fall in blood pressure and a rise in blood urea. Blood sugar was low during or after a relapse.

We wish to thank Drs. L. M. Lockie and G. W. Thorn for their help in this study.

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# Abstract Department

Neural and hormonal influences on bodily activity. Differential factors controlling the heart rate during emotional excitement. Britton, S. W., A. Hinson and W. H. Hall. *Am. J. Physiol.* 93: 473. 1930.

Evidence indicating that growing importance which is related to the frequency of the heart beat and its connection with cardiac output and metabolism is briefly discussed. Experimental analysis is made of the various factors involved in regulation of the heart rate in the cat during an intense emotional reaction attended by moderate muscular activity. Quick reflex changes in rate, i. e., those occurring within a minute or so after excitation, are mediated only through vagal, thoracic, sympathetic and adrenomedullary influences. Any one of these three influences may be eliminated without significant effect on the normal cardiac increments occurring during excitement. The removal of any two factors normally concerned in regulating the activity of the heart is shown markedly to reduce its acceleratory ability—usually by about 50%—following vigorous excitation of the unanesthetized animal. This incapacity persists throughout repeated stimulation extending over many weeks. If all three cardio-regulatory factors are eliminated only negligible variations in rate occur during excitement. In over 100 cases in which normal animals were excited for one and a half minutes the average increase in heart rate was approximately 50% over the basal level. Animals which were subjected to emotional stimulation every second day throughout an eight-weeks' period showed no diminution in cardiac response, and thus exhibited no tolerance towards the excitation.—Authors' Summary.

Seasonal variations in survival of adrenalectomized animals. Britton, S. W., *Am. J. Physiol.* 93: 637. 1930.

The effects of adrenalectomy were studied in the marmot (*Arctomys monax*). In the summer these animals rapidly succumb—usually within ten days—following removal of both adrenal glands. Indefinitely long periods of survival are, however, observed—extending at least over a few months—in animals operated on during the winter. The marmot is very active in summer, and its blood sugar at this time is high and normally between 120-190 mgm. per 100 cc. During the colder weather, although hibernation does not usually occur in captivity, these animals show much less activity and their blood sugar is much reduced—particularly so in the case of adrenalectomized animals. The body temperature also reaches lower levels. The greatly protracted survival periods observed in winter in marmots deprived of adrenal tissues are possibly referable to reduced metabolic activities.—Author's Abst.

Seasonal variations in survival after adrenalectomy. Britton, S. W., *Am. J. Physiol.* 94: 686. 1930.

The marmot (*Arctomys monax*) survives adrenalectomy for 2 to 10 days only when operated on between April and November, or during the normal active period for this hibernating type. Animals which are adrenalectomized during the winter months, when normally inactive or dormant, suffer no immediate ill effects from the operation, and may survive in good health for several months. At the usual time of awakening to activity in April such animals show severe signs of adrenal insufficiency and quickly succumb. The blood sugar, body temperature and heart rate of the marmot were found to be considerably lower during the normal period of dormancy than in summer. There is also a much diminished energy output during hibernation. The intimate relationship of the adrenal glands to metabolism is briefly discussed.—Author's Summary.

Some observations on adrenaline action on the pulse (*Alcune osservazioni intorno all' azione dell' adrenalina sul polso*). Canziani, G., *Riv. di pat. nerv.* 35: 183. 1930.

Adrenaline effects upon the blood pressure can be employed for diagnostic purposes because of their relative constancy. The pulse rate should not be used, because of its irregular and inconstant response.—G. Coronedi.

**The mechanism of epinephrine action. VII. Changes in the glycogen, lactic acid and phosphate content of muscle.** Cori, Gerty T., *Am. J. Physiol.* 94: 557. 1930.

The glycogen content of the right and left gastrocnemius muscle, when extirpated at 30 minute intervals from rats under amytal anesthesia, was found to be of the same magnitude. When after extirpation of the first muscle epinephrine was injected either subcutaneously or by means of an intravenous infusion at a constant rate, a definite reduction in the glycogen content of the second muscle was always encountered. Twenty and 40 minutes after epinephrine injection the phospho-creatine content of muscle was practically unchanged, the inorganic phosphates showed a slight decrease and the lactic acid content of muscle and of blood was markedly elevated.

—Author's Summary.

**Addison's disease associated with congenital absence of suprarenal glands.** Crosby, E. H., *Arch. Path.* 10: 38. 1930. *Abst., J. A. M. A.* 95: 754.

The case of a woman who died at the age of 35 years is reported. At necropsy no gross evidence of suprarenal tissue could be discovered. Microscopically, small islands of suprarenal cortex were found near the superior poles of the kidneys embedded in retroperitoneal fat. It is evident that in cases such as this the embryonic development of the suprarenal gland has been faulty, but that cortical and medullary tissue has existed in sufficient amount to sustain life for many years, finally to become exhausted, a condition resulting in typical Addison's disease and death.

**The mechanism of adrenalin glycemia.** Dworkin, S., *Am. J. Physiol.* 93: 646. 1930.

Recent work (Cori and Cori) on the function of adrenalin in carbohydrate metabolism indicates that the adrenalin hyperglycemia is due to some inhibitory action on peripheral sugar utilization, rather than to conversion and release of stored glycogen. These conclusions have been adduced from experiments with rather large amounts of adrenalin, administered subcutaneously and assumed to be absorbed at a slow rate. We have studied the effects of much smaller quantities of adrenalin—0.001 to 0.004 mgm. per kgm.—injected intravenously, in single doses. Most of the experiments were carried out in cats under amytal anesthesia; a few in normal cats, and in dogs. Provided that the blood sugar level to start with was below 130 mgm.%, there was rarely found, with the amounts of adrenalin used, an increase in blood sugar beyond the renal threshold, or above 70 mgm. per 100 cc. In many experiments the denervated heart was used as an indication of the presence of adrenalin in the blood stream. When, under these conditions, small amounts of adrenalin were injected intravenously (or liberated by splanchnic stimulation) the duration of the increase in the heart rate never exceeded 10 minutes; often the peak was reached in less than 3 minutes; and the glycemia sometimes outlasted the heart rate increase by 40 minutes to 3 hours. If adrenalin, as such, produced the glycemia, it must have exerted its action in a few minutes—a view hardly compatible with the idea that adrenalin raises blood sugar by decreasing sugar utilization. There is, of course, the possibility that the adrenalin, quickly removed from the circulation, remained for a long time in the peripheral tissues; proof of this has not been furnished. In any case, it is obvious that the effects from small, intravenous doses of adrenalin are different from those obtained with the amounts referred to above. The fact that splanchnic stimulations give results similar to those obtained with the small amounts indicates that such quantities more nearly correspond to the physiological activity of the adrenal glands.—Author's Abst.

**A further study of the hormone of the adrenal cortex.** Hartman, F. A. and K. A. Brownell, *Am. J. Physiol.* 93: 655. 1930.

The potency of the extracts used by the authors has been tested by their ability to prolong the lives of completely adrenalectomized cats. As controls 8 cats have been injected every 4 hours with a small quantity of 0.9% NaCl solution and 7 cats twice daily with 6 cc. of the same solution. These cats lived an average of 6.2 days, ranging from 1.5 to 10.3 days. In addition 20 animals were adrenalectomized but not injected. They lived an average of 11.5 days, ranging from 2 to 35 days. The average of 35 control cats was

9.2 days. The following tentative conclusions have been reached in regard to the cortical hormone. Keeping the whole adrenal on ice or at about 35°C. for 18 hours before extraction seems to destroy the hormone or produce a deleterious substance which offsets its value. Preserving the gland on ice in the absence of oxygen is more satisfactory. Acetone, apparently, does not precipitate the hormone. The hormone seems to be destroyed by heating to 80°C. for 5 minutes and by dilute alkali. The activity is preserved better by separating the cortex from the medulla and by preservation at a low temperature, if the tissue is to be kept some time before extraction.

—Authors' Abst.

The effect of extracts of suprarenal cortex on the blood calcium. Mirvish, L. and L. P. Bosman, Brit. J. Exper. Biol. 6: 350. 1929. Abst., Physiol. Absts. 15: 314.

Injection of alcoholic extract from bovine suprarenal cortex lowers the blood calcium content of rabbits by about 30%. A parallel is drawn between this and the calcium-reducing effect of ovarian secretion. Though no physico-chemical tests have been made, it is suggested that this suprarenal hormone is identical with the calcium-reducing hormone of ovary and corpus luteum. It is claimed that this investigation "established a definite relationship between the ovary and the suprarenal cortex."

On adrenal virilism (Sur virilismo sessuale). Ricci, E., Policlinico (sez. prat.) 35: 1881. 1928.

A description is given of a case of adrenal virilism in a 34-year-old woman. There were typical modifications in the voice and the temperament, and an increased libido. A large neoplasm in the right adrenal region was responsible.—G. Coronedi.

The effects of intense x-ray irradiation of the suprarenal gland. Rogers, F. T. and C. L. Martin, Am. J. Physiol. 93: 684. 1930.

The direct application of x-rays of an intensity estimated as three and one-half human erythema doses to the one exposed adrenal gland of dogs, after the excision of the other gland, produced no subsequent changes in the gland, except a slight fibrosis. No functional disturbances appeared in these animals during a period of observation of from 3 to 12 months after the irradiation. The application of six to eight doses to the adrenal gland produced no observable functional disorders in dogs kept three months after irradiation, although fibrous proliferation in the gland can be demonstrated microscopically. Adrenal deficiency symptoms can be induced in dogs by the surgical excision of one gland and giving excessive x-ray doses to the remaining gland, but the lapse of several months may be required for their appearance. These effects are as follows: the gradual onset of a progressive muscular weakness, depression of metabolism, terminal lowering of the blood chlorides and death. Heavy dosage of x-rays to the exposed adrenal gland induces degenerative changes, first in the medulla of the gland, and then of the zona reticularis and zona glomerulosa and an extensive proliferation of fibrous tissue throughout the gland.—Authors' Abst.

Atrophy of the adrenals associated with Addison's disease. Susman, W., J. Path. & Bact. 33: 749. 1930.

Five cases of Addison's disease are recorded in which the lesion in the adrenals was a simple or fibroid atrophy, and it is found that about one-fifth of all cases of Addison's disease are associated with this form of lesion. Atrophy of the adrenals as a cause of Addison's disease appears to be more common in England than elsewhere. In cases of atrophy, both cortex and medulla are usually affected, but a lesion of the cortex is the more constant and may be the sole feature in some cases.—Author's Summary.

Addison's disease in a Negro. Report of a case. Sala, A. M. and M. Jacobi. Arch. Int. Med. 40: 375. 1930.

Including the present one, only five cases of tuberculous involvement of the suprarenal glands in Negroes are on record, a rather surprising fact in view of the frequency of pulmonary and miliary tuberculosis in the race. In this

series of cases, females were more frequently affected than males (3:2), as against an average of (2:1) greater frequency in males among white people. The age incidence in these cases was somewhat higher than in white people. Pigmentary changes did occur in the cases of considerable duration. These involved areas usually uninvolved in white people (nail-beds, soles and palms), although this distribution may be due merely to the more ready recognition of pigmentary changes in these areas in colored patients. Changes in general pigmentation may become extreme and extensive. In the acute forms, pigmentary changes may be absent. The course in the cases recorded was more rapid than in white people. Nervous symptoms were not prominent in any case. Laryngeal symptoms—hoarseness, pain on speaking and a choking sensation—were prominent, or even presenting, symptoms in this group of cases. No local evidence to explain these symptoms was present. Asthenia was a prominent symptom; anorexia was marked. In all cases, except in those in which pigmentary changes and gastro-intestinal and asthenic symptoms were marked, the diagnosis, always difficult to make in white people, was extremely difficult; in the acute case, it was not often made except at autopsy.

—Authors' Summary.

**Adrenalectomy and muscle fatigue.** Stevens, H. C. and J. M. Rogoff. *Am. J. Physiol.* 93: 691. 1930.

Experiments were made upon decerebrate, adrenalectomized cats, in which the fatigue curve of the gastrocnemius muscle was studied. Curves obtained during the period of survival in good health, following double adrenalectomy, did not differ materially from curves obtained with animals that were not subjected to adrenalectomy. The behavior of cats during the following decerebration, the blood pressure and respiratory response, the specific reactions of the gastrocnemius muscle as evidenced by the fatigue curve, the component phases of the twitch myogram and the chronaxie of the tibial nerve and the muscle in the adrenalectomized cats were compared with similar observations, made under the same conditions, in control non-adrenalectomized animals.

—Authors' Abst.

**Studies on suprarenal insufficiency. VIII. The blood volume of the rat in suprarenal insufficiency, anaphylactic shock and histamine shock.** Wyman, L. C. and Caroline tum Suden. *Am. J. Physiol.* 94: 579. 1930.

In 23 normal rats the per cent of plasma of the blood was from 51.7 to 60.7, averaging 56.3 per cent. The blood volume was from 6.6 to 9.6 per cent of the body weight, averaging 7.6 per cent. Following a control blank operation blood volume determinations were within the normal range. In suprarenalectomized rats having autoplasmic cortical transplants but no demonstrable chromaffin tissue blood volume determinations were within the normal range. In suprarenalectomized rats which possessed gross accessory cortical tissue and before the appearance of severe symptoms in those which died later of insufficiency the blood volume remained unchanged except for normal fluctuations. After severe symptoms of suprarenal insufficiency had appeared or during the final stages of insufficiency there was a reduction in the blood volume, due chiefly to a reduction in the plasma volume. It is suggested that inability to maintain capillary tone and normal permeability, probably due to lack of medullary suprarenal secretion, and resulting in reduction of plasma volume, is the chief factor in increased susceptibility of suprarenalectomized rats to anaphylactic and histamine shock.—Authors' Summary.

**Metabolism in dementia praecox.** Stevenson, G. H. and J. C. Thomas. *Canad. M. A. J.* 22: 636. 1930.

Study of 16 cases showed no constant or definite deviation from normality.—A. T. C.

**Pathological precocities (Precocita patologiche).** Antognetti, L. *Endocrinol. e patol. constit.* 4: 297. 1929.

Five cases of precocious sexual development are described, in two of which there was a precocious commencement of the menstrual rhythm with indications of hypothyroidism. Three cases of precocious matronism (Pende's syndrome) are described.—G. Coronedi.

A pressor substance obtained from the prostate gland of the bull. Collip, J. B. Tr. Roy. Soc. Canada (Sect. V, Biol. sc.) 23: 165. 1929.

An epinephrine-like substance has been demonstrated in extracts made from the prostate gland of the bull. Its preparation is described and effects similar to epinephrine demonstrated as regards blood pressure (and cocaine sensitization) uterine contractions and blood sugar.—R. G. H.

Ovary-stimulating hormone of the placenta. Collip, J. B. Nature, 125: 444. 1930. Abst., Chem. Absts. 24: 3824.

Collip describes a crystalline substance obtained from extracts of placenta. It is protein- and lipid-free and, when given to experimental animals, is active in bringing about prematurity of young rats and in prolonging the gestation period of adult rats. The effect of the extract of placenta is being studied in certain clinical cases.

Effect of ovarian extract on motility of rhythmically contracting uterus. Durrant, E. P. Am. J. Physiol. 93: 645. 1930.

The rhythmic contractions of excised rat uterus in oxygenated Tyrode's solution were recorded from the entire horn and from ovarian and cervical ends separately. While contracting normally the segments of uterus were subjected to the action of 0.1 per cent, 0.2 per cent and 0.3 per cent of different commercial ovarian extracts. Of 13 animals thus studied, all but one responded with diminished activity up to complete inhibition with the largest dosage. Similar dosage had no effect on segments of intestine from the same animal. —Author's Abst.

Effects of ovarian extracts on voluntary activity of white rat. Durrant, E. P. Am. J. Physiol. 93: 646. 1930.

Eighteen mature female white rats were kept in self-registering revolving cages until the cyclic variations in activity associated with oestrus were clearly shown on graphs prepared from the daily runs. One-half were then injected subcutaneously with 0.2 cc. of a pharmaceutical ovarian extract each day. The other half were similarly treated with distilled water. The treatment, continued for 24 days, was without effect on the rhythm of activity but produced a marked disturbance in the vaginal mucosa.—Author's Abst.

Multiple ovaries and oestrus. Friedman, J. L. and L. B. Nice. Am. J. Physiol. 93: 650. 1930.

Twenty-one female white rats each received an ovary from two other white rats so that each animal had four ovaries—its own pair and one from each of two others. The oestrus of these rats was studied by the smear method before and after transplantation. After transplantation the cycles were found irregular and much more frequent than before. The activity of these rats does not correspond closely to the oestrus cycle.—Authors' Abst.

Influence of follicular and corpus luteum hormones on the uterine endometrium of rabbits and monkeys. Hisaw, F. L., R. K. Meyer, S. Leonard and H. L. Fevold. Am. J. Physiol. 93: 659. 1930.

Extracts of sow corpora lutea yield a crystalline and a non-crystalline fraction which produce characteristic physiological reactions in experimental animals. The crystalline fraction causes relaxation of the pelvic ligaments of castrated female guinea pigs while the non-crystalline fraction promotes several reactions generally accredited to the corpus luteum, two of which are the development of the progestational endometrium in the uterus of castrated rabbits and the premenstrual endometrium in the uterus of castrated monkeys. Relaxation as well as progestational and premenstrual changes in the uterine endometrium require the action of both the follicular and corpus luteum hormones, neither being able to elicit positive results in castrated animals when given alone. Neither can the corpus luteum hormones promote and preserve the relaxed, progestational, or premenstrual conditions over an extended period in the absence of the follicular hormone. The corpus luteum hormone alone



will not prevent menstruation in a castrated monkey previously treated with follicular hormone nor prevent the return of the progestational endometrium of a rabbit to a castrated condition. These reactions seem to be of a "one two" nature, i.e., the follicular hormone must act first, followed by the corpus luteum hormone, and both must be present to prolong the effect. The crystalline fraction of the corpus luteum which produces the relaxation of the pelvic ligaments of the guinea pig bears a qualitative relationship to the follicular hormone, while the non-crystalline fraction which produces the uterine changes bears a quantitative relationship to the oestrus producing hormone. That is, large doses of follicular hormone do not inhibit the action of the relaxative hormone, but in the case of the non-crystalline fraction large doses of oestrin will prevent its action on the uterus.—Authors' Abst.

The relation of gonadal condition to erythrocyte number in fowls. Juhn, Mary and L. V. Domm. *Am. J. Physiol.* 94: 656. 1930.

The erythrocyte number was determined in 80 brown leghorns, 40 males and 40 females, at intervals from the day after hatching to 16 months of age. A definite sex dimorphism in the number of red cells was noted confirming other observations cited. The juvenile and the gonadectomized bird of either sex and the mature female all show a similar erythrocyte number. The number of red cells is significantly higher in the adult male, the increase becomes apparent at the time of sexual maturity. Thirty red counts carried out in poulards show that the modifications in the male direction noted after removal of the left ovary can now be extended to include the erythrocyte number which equals that of the adult male.—Authors' Summary.

Ovarial function and lipid content (ovarialfunktion und Lipoidhaushalt; über die Verteilung des Blutcholesterins in freies und verestertes Cholesterin in den verschiedenen Funktionsphasen der Keimdrüse; der Gesamtfettsäuregehalt des Blutes bei regelmässiger, bei unregelmässiger und fehlender Ovarialfunktion). III. Kaufmann, C. and O. Mühlbock. *Arch. Gynäk.* 139: 254. 1929. Abst., *Chem. Absts.* 24: 3545.

During menstruation the total cholesterol content of the blood serum decreases, and the change is due largely to a decrease in free cholesterol. There are also changes in the relation of cholesterol esters to free cholesterol. At the time of menstruation 85-90 per cent of the total cholesterol is in the ester form and at other times 70 per cent. The free cholesterol also shows a greater variation than the cholesterol in ester form. The lecithin content of the blood serum is independent of the cholesterol content and does not show any definite alterations during menstruation. Increased amounts of total fatty acids are noted in the circulating blood during menstruation. Removal of the ovaries does not produce a regular alteration in the total lipid content of the blood serum or of the distribution of the individual components. In the physiological climacteric increased cholesterol, lecithin and fatty acid content of the blood serum are occasionally noted.

A new demonstration of physiological activity of corpus luteum. Macht, D. I. *Am. J. Physiol.* 93: 671. 1930.

It has been pointed out by Siddall and others that the weight of the uterus in the white mouse bears a definite ratio to the weight of the adult, non-pregnant animals, this ratio being over 400. Frank and other investigators have found that when white mice are given injections of the follicular hormone, the uterus is hypertrophied, and Siddall established that in such cases the ratio of the weights of the uterus and the whole animal is much below the normal ratio 400. In the present investigation, the writer attempted to determine whether the corpus luteum hormone would counteract the effects of follicular hormone on the size and weight of the uterus. Three sets of experiments were carried on simultaneously. In the first set, mice were fed a normal diet without the administration of ovarian extracts. In the second set, mice were given the same food but received a number of injections of the follicular hormone. In the third set, mice were injected simultaneously with the follicular hormone and corpus luteum extracts. After various periods of time, ranging from 10 days to two weeks and more, the animals were killed, the uteri dissected, and the relation of the uterine weight to the weight of the whole animals was

determined. In the normal controls, this ratio was never below 400 and was usually higher than that figure. In the mice which received injections of follicular extracts alone, a definite hypertrophy of the uteri was noted in most cases, and the ratio of the uterus to the body weight was much below 400. In the third set of experiments the mice which received simultaneous injections of the follicular and corpus luteum extracts showed no hypertrophy of the uteri and gave the same ratio of the weights as the normal controls. Such triple sets of experiments were performed many times, always giving the same results. It therefore appears that injections of corpus luteum extracts counteract the hypertrophy-producing effects of follicular extracts. Feeding experiments with the ovarian products were also conducted and gave similar results, although a much longer period of time was necessary.—Author's Abst.

**Studies of female genital hypoplasia.** Meaker, S. R. J. A. M. A. 95: 468. 1930. Abst., A. M. A.

The author asserts that female genital hypoplasia is a common condition and a major factor in the causation of sterility. The immediate cause of such hypoplasia is most commonly a congenital insufficiency of the anterior lobe of the pituitary. The diagnosis of established hypoplasia in adult women depends mainly on pelvic examination and the recognition of characteristic stigmas in the uterus. Treatment of established genital hypoplasia is at the present time wholly ineffectual. The diagnosis of incipient or threatened hypoplasia in adolescent girls depends, first, on the recognition of abnormal menstrual behavior, and, secondly, on the identification of depressing constitutional factors, both endocrine and non-endocrine. The treatment of incipient or threatened hypoplasia consists in the elimination of all depressing constitutional factors, and is a hopeful undertaking. In the management of the adolescent cases there exists a new and important opportunity for the practice of preventive gynecology. Both non-endocrine and endocrine abnormalities require to be corrected. The general hygiene of the modern girl leaves much to be desired. Milder grades of anemia are frequent and appear to have a particular depressing effect on the reproductive system. Chronic focal infection contributes demonstrably to disturbance of the endocrine functions. In occasional cases congenital syphilis, rickets, lesions of the central nervous system, and other disease entities require treatment on the ground of their harmful influence on the metabolic level, as well as on their own merits. The mechanism of endocrine treatment in the adolescent patient is primarily substitution, with an excellent chance of secondary homostimulation. Monoglandular therapy gives better results than pluriglandular; if the primary focus of failure is normalized, responsive disturbances in other glands tend to regulate themselves. The gland required is usually the anterior lobe of the pituitary, occasionally the thyroid, and never the ovary. Success depends on the use of potent preparations in adequate dosage.

**The effect of testicular extracts on the blood calcium.** Mirvish, L. and L. P. Bosman. Brit. J. Exper. Biol. 6: 355. 1929. Abst., Physiol. Absts. 15: 316.

Injection of alcoholic extract of testis equal to about 200 gm. fresh tissue, lowers the calcium content of rabbit blood by about 30 per cent. The character of the fall is the same as that obtained after ovarian injection, though the amount required is about 10 times greater. When the extract was purified with ether, no fall was recorded. It is suggested that the presence of such a physiological reaction might be utilized to extract and purify the testicular hormone.

**Ovarian reaction in young rat to action of urine of pregnant women.** Malinengo, L. Clin. obstet. 32: 385. 1930. Abst., J. A. M. A. 95: 1215.

The degree of reaction of the ovary of the young rat to the action of the urine of a pregnant woman is, within strict limits, parallel to the dose of the injected substance. The possibility of securing with small doses of urine a follicular phase, and with heavy doses massive hyperluteinization of the ovary, awakens doubt as to the correctness of the principles on which Evans and Simpson base their theory in regard to the plurality of antehypophyseal hormones.

**The preparation of the crystalline follicular ovarian hormone: Theelin.** Veler, C. D., S. Thayer and E. A. Doisy. *J. Biol. Chem.* 87: 357. 1930.

A quantity production procedure for the preparation of theelin is described. Essentially the procedure depends upon the fact that theelin, which behaves as a very weak acid, may be extracted from organic solvents with dilute NaOH solutions, and then in turn may be extracted from the alkaline solution by certain organic solvents.—Authors' Summary.

**Preparation of female sex-hormone (Zur Darstellung des weiblichen sexual Hormons).** Zondek, B. and C. van Eweyk. *Klin. Wchnschr.* 9: 1436. 1930.

Two methods of separating the hormone from pregnant urine (a) absorption with charcoal and (b) precipitation by salts of a heavy metal, lead acetate for example, are described. A larger degree of recovery is had by the second method. By repeated solution and evaporation the hormone can be highly purified and so concentrated that 1 cc. of a watery solution may contain as much as 8000 oestrus producing units.—E. P. D.

**Influence of lipid hypophyseal hormone on deaminization in the organism (Über den Einfluss eines lipoiden hypophysären Hormons auf die Desaminierungsprozesse in den Organen).** Agnoli, R. *Arch. f. experi. Path. u. Pharmakol.* 134: 74. 1928. *Abst., Biol. Absts.* 3: 1196.

The rate of deaminization in animals was determined by estimating the amount of amino acids in the blood after intravenous injection of known amounts of glycocholl. An extract of posterior lobe of the hypophysis (ox) had no influence on the process. Commercial extracts (hypophysin of Höchst and endopituitrin of the Serotherapeutic Institute of Milan) were similarly without effect. Fresh extract of the whole gland (ox) had a definite action on the process, deaminization undergoing a noticeable acceleration. Lipoid extracts of whole dried gland (ox) and fresh gland (swine) exhibited a more marked accelerating action. There must be a hormone in the anterior lobe of the hypophysis, perhaps corresponding to the so-called theelin of Robertson, which possesses a stimulating action on intermediate protein metabolism.

**The influence of different parts of the hypophysis upon size growth of Rana tadpoles.** Allen, B. M. *Physiol. Zool.* 1: 143. 1928. *Abst., Biol. Absts.* 3: 1197.

Living anterior, intermediate, and posterior lobe material of the hypophysis of adult frogs was implanted separately into thyroidectomized and into hypophysectomized tadpoles of the same species, *Rana aurora draytoni*. The anterior lobe of the hypophysis is shown to be alone concerned in stimulating growth. It causes the hypophysectomized tadpoles to attain normal size even though previously much retarded. Implantation of the intermediate or posterior lobes of the hypophysis into hypophysectomized tadpoles does not cause them to resume normal growth. Implantation of the anterior lobe of the hypophysis into thyroidectomized tadpoles causes them to show a normal growth rate only slightly greater than that shown by normal controls or thyroidectomized tadpoles into which such implantation has not been made. These results were not due to nutritional absorption of the implant, because the latter was maintained in a living and functional condition and because implants of intermediate and posterior lobe of the hypophysis and of liver failed to stimulate growth, in spite of the fact that the intermediate lobe at least showed its activity by producing very striking color changes.

**Diabetes insipidus during pregnancy.** Anselmino, K. J. and F. Hoffmann. *Zentralbl. f. Gynäk.* 54: 2061. 1930. *Abst., J. A. M. A.* 95: 1388.

Anselmino and Hoffmann report a case in which diabetes insipidus became manifest in two successive pregnancies and disappeared again during the first day of the puerperium. The diagnosis diabetes insipidus was based on the determination of the sodium chloride content of the blood and of the urine during thirst periods and during water tests. The examinations of the blood and of the urine revealed that this case of diabetes insipidus was of the type that is characterized by hypochloremia and hyperchloruria. On the basis of the Hann-Jacobi theory, according to which diabetes insipidus is due to a dis-

turbance in the equilibrium between the secretions of the anterior lobe of the hypophysis and its posterior lobe (an excessive secretion of the anterior lobe causes diabetes insipidus) the authors reason that in this case the isolated manifestation of the disease during two gravidities may be explained as follows: A syphilitic infection caused a functional deficiency of the posterior lobe. Under ordinary conditions this deficiency was latent. However, during pregnancy the functional capacity of the organ was taxed more and the deficiency became manifest.

**Hypopituitarism with special reference to its sexual manifestations.** Berry, N. E. *Canad. M. A. J.* 22: 354. 1930.

A report of a case of Froelich's syndrome.—A. T. C.

**Galactorrhœa in acromegaly (Galactonhée chez une acromégale).** Carnot, P. and Bouttier. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 54: 392. 1930. *Abst., J. A. M. A.* 94: 2028.

In Carnot and Bouttier's patient, aged 27, symptoms of increasing acromegaly had been noted for several years. The symptoms consisted of an increase in the size of the hands and feet, severe pains and increasing size of the maxilla, hypertrophy of the tongue, enlargement of the sella turcica, and thickening of the bones of the skull. Menstruation had been irregular and often deficient for the past three years, coincident, however, with a persistent lactic secretion from the breast. Injection of the urine of the patient into not fully developed or castrated female mice and rats and male rats did not stimulate the development or activities of the genitalia or hormones of hypophyseal origin. According to the authors, this points toward separate kinds of hormones. Anterior lobe hormones stimulating mammary secretion may be distinguished from those stimulating activity of the genito-urinary tract.

**The functions of the pituitary in the dog. II (Experimentelle Untersuchung der Hypophysenfunktion beim Hunde-II).** Koster, S. *Arch. f. d. ges. physiol.* 224: 212. 1930. *Abst., Physiol. Absts.* 15: 313.

The endocrine glands were examined in dogs in which the pituitary had been removed (experiments previously reported). The thymus was rather heavier than normal, and the suprarenals showed no definite changes in weight. All the other endocrine organs were smaller and lighter than in control animals.

**The effects of extracts of the posterior hypophysis on the water interchange in muscle.** Steggerda, F. R. *Am. J. Physiol.* 93: 691. 1930.

Measurements were made on the effects of surgical pituitrin, vasopressin and pitocin on the water interchange of the isolated frog's gastrocnemius muscle. In all cases the left gastrocnemius served as the experimental muscle, whereas the right gastrocnemius of the same frog was the control. After isolation, both the right and left gastrocnemius muscles were placed in normal Ringer's solution for one-half hour. Weighings of the muscles were then made on an analytical balance, after which the muscles were submerged in Ringer's solutions of various strengths. In all cases extracts of posterior pituitary were added to the solution containing the experimental muscle. Successive weighings were made at intervals over a period of more than two hours, whereby percentage variations in muscle weights could be noted and plotted. Ninety experiments were performed, using normal, hypotonic and hypertonic Ringer's solutions containing different amounts of surgical pituitrin, vasopressin and pitocin. Plotted curves show no appreciable change in weight between the experimental and control muscles. The results tend to show that extracts of the posterior hypophysis have no effect on the permeability of the isolated frog's gastrocnemius to water.—Author's *Abst.*

**Use of extracts from posterior lobe of hypophysis in local anesthesia (Über die anwendung von Hypophysenhinterlappenextrakten in der Lokalanästhesie).** Wermer, P. *Klin. Wchnschr.* 9: 779. 1930. *Abst., J. A. M. A.* 95: 308.

Wermer points out that in local anesthesia cocaine or procaine hydrochloride is usually combined with epinephrine. But because epinephrine frequently causes complications the author made tests to determine whether this

suprarenal extract could be replaced by extracts from the posterior lobe of the hypophysis. He described his experiments and then he relates that this mixture of procaine hydrochloride with the extract from the posterior lobe of the hypophysis was successfully employed for local anesthesia, especially in laryngologic operations, in tonsillectomy and in dentistry. It has also been used in resection of the stomach. Among the patients on whom the hypophyseal extract was employed were several with endocarditis, valvular defects, hypertension or hyperthyroidism and also numerous patients who were more than 70 years of age. For surgical interventions the dosage is from 5 to 10 Vögtlin units of hypophyseal extract to 250 cc. of a solution of procaine hydrochloride; for tonsillectomies from 1 to 3 units for 30 cc. of procaine hydrochloride solution; and in dentistry  $\frac{1}{2}$  unit for 2 cc. or a 2 per cent solution. The hypophyseal extract contracts the capillaries mainly. Complications did not develop. Their absence was especially noticeable in dentistry and in laryngologic operations. Many dental patients in whom epinephrine had always caused unpleasant manifestations found the mixture of procaine hydrochloride with hypophyseal extract entirely agreeable. In major operations the patients are not troubled by palpitation of the heart, and the pulse rate sometimes even shows a decrease. Intestinal complications were likewise absent. The author recommends the use of hypophyseal extract in all forms of infiltration and regional anesthesia. He considers it especially valuable in cases in which the suprarenal extract is contraindicated on account of its influence on the circulation and on the metabolism.

The hormones of the anterior pituitary. IV. Preparation of follicle-maturing hormone (Prolan A). Method of clinical urine analysis as a test for Prolan (Ueber die Hormone des Hypophysenvorderlappens. IV. Darstellung des Follikelreifungshormons (Prolan A). Metodik der Klinischen Harnanalyse zum Nachweis des Prolan). Zondek, B. Klin. Wchnschr. 9: 1207. 1930.

Urine is acidified with acetic acid precipitated with 96 per cent alcohol and the precipitate purified by ether. The ether is removed and the purified precipitate dissolved in water. The dissolved substance is then further treated with alcohol and ether until a high degree of purification is reached. Biological tests based on the characteristic reactions of the ovary show that Prolan can be obtained from both non-pregnant and pregnant urine.—E. P. D.

The effect of cholecystokinin on the human gall bladder. Ivy, A. C., G. E. Drewyer and B. H. Orndoff. Am. J. Physiol. 93: 661. 1930.

A "purified" solution of cholecystokinin (1860 preparation) was prepared and shown to be neither toxic in the dog nor antigenic in the guinea pig. It was free of vaso-dilatin and active in the dog in 3 mgm. doses. From 25 to 30 mgm. of this material has been injected intravenously at ten-minute intervals into 5 normal subjects and 3 dispensary patients in which gall-bladder disease had been suspected. The gall bladder was visualized with phenoltetraiodophthalein; of the 5 normal subjects, all but one manifested some degree of gall-bladder evacuation when injected every 10 minutes for one hour. On one the evacuation was complete, in the other three it was partial. Two of the 5 felt "light-headed" about one hour after completing the injections, which sensation disappeared within the course of 30 minutes, no other symptoms being complained of. Only 3 doses were given at 10-minute intervals to the three dispensary patients. Two of the 3 showed a definite decrease in the size of the gall-bladder shadow, one of them having a pericholecystitis. Further work on the human will not be undertaken until the product is further purified. —Authors' Abst.

The surgical problems presented by the diabetic. Bazin, A. T. Canad. M. A. J. 23: 146. 1930.

Provided that the diabetic state is recognized and properly controlled, diabetes does not influence the surgical treatment and prognosis. In the Montreal General Hospital in 1929 the diabetics showed 221 cases exhibiting complications and associated conditions. Of these 87 were surgical and 73 went to operation. There were 2 deaths. The importance of accurate biochemical studies during control is emphasized. Control by urine analysis is imperfect and often inadequate, as is also determination of a fasting blood sugar. A blood sugar time curve is necessary.—A. T. C.

A brief review of certain physiological-properties of insulin. Best, C. H. *Canad. M. A. J.* 23: 141. 1930.

The review deals with the following: site of production; liberation; action; interference with the action; preparation and properties; and insulin and diabetic mortality.—A. T. C.

Clinical functional test of the islands and the question of insular genesis of obesity (*Zur klinischen Funktionsprüfung des Inselapparates und zur Frage der insulären Genese der Fettsucht*). Depisch, F. and R. Hasenöhr. *Klin. Wchnschr.* 9: 215. 1930.

The work is based on the observations of Aschner that the difference between capillary and venous blood sugar after a glucose meal represents the insulogenic function and also the ability of the tissues to use glucose; thus the difference between these two levels should be the functional capacity of the islands: The authors state that contrary to Aschner, the niveau difference has not a special significance. In animals with extirpated pancreas, thus a high blood sugar, after insulin injection the venous sugar rises due to washing out from the tissues so that it rises even above the arterial. The question of obesity the authors feel cannot be explained wholly by increased insulogenic function.—H. J. J.

A preliminary note on the detection of an insular hormone in the duodenum. Laughton, N. B. and A. Bruce Macallum. *Canad. M. A. J.* 23: 348. 1930.

Confirming Heller the authors find that injection of extracts of duodenal mucosa into normal rabbits and dogs prior to injection of half a gram of glucose per kilo body weight lessens the usual degree of hyperglucaemia. It has no effect on the blood sugar of depancreatized dogs with marked hyperglucaemia, so that the extracts do not contain insulin. Since pure secretin has no such effect, and insulin is excluded, there would appear to be a substance in normal duodenal mucosa which stimulates the production of insulin. This suggests that insular failure may result from excessive stimulation of the islets by the duodenal hormone produced as a result of excessive sugar intake over long periods, and secondly, that inflammatory conditions in the duodenum may lead to a deficiency in the hormone followed by diminished activity in insulin output whence a hyperglucaemia. The extract is water-clear and gives none of the protein color reactions.—A. T. C.

The action of intravenous sugar injections on ketonuria in diabetes mellitus and in diabetic coma (*Ueber die Wirkung von intravenösen Zuckerinjektionen auf die Ketonurie bei Diabetes mellitus und bei diabetischem Koma*). Lorant, J. S. and E. Frochlich. *Klin. Wchnschr.* 9: 213. 1930.

Intravenous injection of sugar causes a considerable rise of ketone bodies in diabetics also in coma which persists at least for two hours. The author explains this rise by the transport of the ketones through the injected solution. The author thinks that these injections in coma are bad in so far as they prolong the desugarization and force one to use larger insulin doses, which in turn might cause hypoglycemia together with the first point mentioned.

—H. J. J.

Clinical investigations into the effect of intravenous injections of insulin. II. Hypoglycemic symptoms in normal individuals. Norsted, A., A. Norgaard and Th. E. H. Thaysen. *Acta med. Scandinav.* 73: 125. 1930.

Prominent among the hypoglycemic symptoms are the rise of systolic and fall of diastolic blood pressure, and the increase of pulse rate. The maximal changes in blood pressure and pulse rate are found near the time when the hypoglycemia comes to a stop and the blood sugar concentration begins to rise. A very essential—probably the most important—part of this regulation mechanism is very likely an increased activity of the adrenals. It may be that other endocrine glands take part in this regulation, too. The term "insulinism" is perhaps preferable to "hypoglycemic" symptoms.—Authors' Summary.

An investigation of the antagonism of insulin by posterior pituitary extracts as indicated by changes in gastro-intestinal motility. Quigley, J. P. and B. O. Barnes. *Am. J. Physiol.* 93: 682. 1930.

Employing unanesthetized trained dogs, fasting 20 to 44 hours, the motility of the stomach and colon has been followed by the balloon method. Using highly purified insulin, confirmation has been obtained of a number of the effects on gastro-intestinal motility previously noted from commercial insulin. The effect of pituitrin (Parke, Davis & Co.), oxytocin or vasopressin on gastro-intestinal motility in insulinized or non-insulinized dogs appears to be entirely similar. The optimal dose for the gastric effect is 4 to 8 units intravenously or any of the pituitary preparations. When administered to animals with low spontaneous tone, high spontaneous tone or the hyperactivity of the gut produced by insulin, complete inhibition of tone and motility was the invariable result. The inhibition began 15 to 20 seconds after the administration of the pituitrin. In animals under the influence of insulin the blood sugar level remained constant for 3 to 5 minutes after the injection of pituitrin but rose to or above normal within 10 minutes. The blood sugar fell in the period which followed, during which the gut was recovering from the inhibition. No indication of an augmentation of gastro-intestinal motility was obtained as the result of the administration of pituitary preparations. The mechanism by which pituitrin inhibits the motility of the gut does not appear to be related to its action on carbohydrate metabolism except during the latter part of the inhibition period.—Authors' Abst.

The diagnosis of renal glycosuria. Rabinowitch, I. M. *Canad. M. A. J.* 22: 329. 1930.

During the previous 12 months 3 patients with advanced diabetes were admitted to the Montreal General Hospital; in each case a diagnosis of renal glycosuria had been made less than 2 years previously, in one based upon a sugar time curve made in a hospital. It is considered that for an absolutely correct diagnosis of renal diabetes the following conditions should be fulfilled: There must be no signs nor symptoms of diabetes; there should, ideally, be no family history of diabetes; the figure for blood sugar obtained in the fasting state must always be normal; there must be little or no relationship between the intake and excretion of sugar; the rate of utilization of sugar should be normal; and the individual must not subsequently develop diabetes. Study of a case fulfilling all these conditions is detailed. It is considered that it is unwise to make a diagnosis of renal glycosuria in office practice, and that it is safer to underfeed a normal individual than to overfeed a diabetic. An individual with glycosuria should be regarded as a diabetic until proved otherwise.  
—A. T. C.

Lipodystrophy from insulin injections. Reed, Lucille L., W. E. Anderson and L. B. Mendel. *J. A. M. A.* 95: 395. 1930. Abst., *A. M. A.*

In an effort to determine whether injections of insulin or other substances would cause a lipodystrophy, the authors injected healthy female rats subcutaneously in a pad of fat occurring on the ventral surface of the right leg with 0.6 unit of insulin daily, the dose being divided into three parts. (This dosage is on the basis of 3 units per kgm. of body weight, or 210 units for a 70 kgm. man.) Another group of rats was injected with the same volume of physiologic solution of sodium chloride at the same time in the same location. Still another group received no injections at all. The rats were killed after sixty days and the pelt removed. The amount of subcutaneous fat around the right and left legs was estimated separately for the rats in each group by the method described by Reed, Yamaguchi, Anderson and Mendel for the determination of the fat content of adipose tissue. The variations occurring in the groups injected with insulin or with physiologic solution of sodium chloride suggested that neither substance was influential in changing the amounts of fat stored in the subcutaneous tissues. It is conceivable that the adipose tissues of normal and diabetic organisms react differently to injections of insulin or that in the present instance the injections were discontinued before the lipodystrophy had time to develop. In any event the current hypotheses for the genesis of localized lipodystrophy after insulin injections have not been substantiated under conditions that may be regarded as sufficiently drastic to produce the expected results.

Isolation of a new hormone of the pancreas (Isolement d'une nouvelle hormone pancréatique). Santenols, D., H. Verdier and M. Vidacovitch. Rev. frang. d'endocrinol. 8: 204. 1930.

Working on dogs, over several years and with as rigid experimental discipline as possible, the authors have shown that the pancreas secretes a regulatory hormone affecting the functional activity of the pneumogastric centers. This hormone is found not only in the gland itself and in the blood coming from the gland, but also in the arterial blood of the general circulation. The vagotonizing ability does not belong to insulin but to another hormone secreted by the pancreas. Insulin does not excite the pneumogastric reflexes. The authors were able to extract this vagotonizing hormone of the pancreas, and separated it by the use of alcohol and neutral salts from insulin. They propose to name this substance, at least provisionally, vagotonine. It would appear that the pancreas, through this agency, exerts an important regulatory action on the functional activity of the pneumogastric centers. Resulting from this there is a whole series of physiological actions of vagotonine causing a principle rôle to be attributed to the pancreas in the regulation of activity in different organs innervated by the pneumogastric.

—Authors' Summary—translated.

The alterations in the blood sugar following reflex vagus stimulation (Die Zunahme des Insulingehaltes des Blutes nach reflectorischer Vagus-reizung). Van Goor, H. Arch. néerl. de physiol. 14: 534. 1929. Abst., Physiol. Absts. 15: 309.

Stimulation of the nasal mucosa of rabbits by cigar smoke or rebreathing in man may produce a fall of blood sugar lasting some hours. Insulin was estimated in blood by Ahlgren's method, which depends on the time of reduction of methylene blue in presence of glucose and muscle tissue; mean concentrations of insulin (diluted commercial solution was used) decrease the reduction time, as also does serum after reflex vagus stimulation, including rebreathing. Adrenaline, but not phloridzin, produces a shortening also, but both prevent the insulin reduction, though adrenaline plus insulin without glucose show some shortening. Adrenaline plus phloridzin plus insulin shorten, but not in the absence of glucose. Pituitrin causes shortening also and aids the action of insulin.

The parathyroid and ergosterol hypercalcaemia (Nebenschilddrüsenhormon und Ergosterin-hypercalcaemie). Bischoff, G. Ztschr. f. phys. Chem. 188: 247. 1930. Abst., Physiol. Absts. 15: 315.

Administration of the parathyroid hormone to dogs with hypercalcaemia from overdoses of ergosterol led to a definite fall in the serum calcium. This fall lasted about as long as the rise in serum calcium lasts in normal animals given parathyroid. The premortal fall in serum calcium which occurs with large overdoses of parathyroid hormone in normal animals occurred also in animals suffering from ergosterol poisoning sooner and with smaller doses of parathyroid. If the parathyroid is given in the early stages of ergosterol poisoning, the high serum calcium fall and is kept at the low level for some 24 hours before a rise again occurs, the condition of the dogs being much improved. The parathyroid hormone can thus cause and maintain a lowering of blood calcium under some conditions.

Bone changes in hyperparathyroidism. Compere, E. L. Surg. Gynec. & Obst. 50: 783. 1930.

A case is reported in which a diagnosis of hyperparathyroidism was made on the basis of a syndrome consisting of pain and bowing of the bones of the weight-bearing extremities, osteoporosis of the bones of the skeleton, progressive muscular weakness, elevated serum calcium and lowered serum phosphorus, a negative calcium balance, and a palpable nodule in the lower pole of the right lobe of the thyroid gland. An enlarged adenomatous parathyroid gland was removed at operation and a second gland was removed from the opposite lobe of the thyroid gland and found to be normal. Symptom improvement followed resection of this tumor. A résumé of 11 other cases may be included under the definition of hyperparathyroidism. All of the cases have been recent.



generalized osteoporosis. Areas of rarefaction resembling bone cysts were reported in 6 of these cases and in 3 cases diagnoses of giant cell tumors were made. Spontaneous fractures had occurred in 5 of the cases. Tumors of the parathyroid glands were removed at operation from 8 of these patients and, in another case where no tumor was found, two normal glands were removed. One patient died in tetany after removal of a parathyroid tumor and one normal parathyroid gland. Symptomatic improvement was noted in all of the other cases, after removal of the parathyroid tumor. In 4 of these cases the authors reported roentgenological evidence of increased density of the bones of the skeleton. The symptomatic improvement in these cases, the chemical evidence of increased calcium retention, and the x-ray evidence of increased density of the bones in a few cases which had been followed for a long period after operation are results which, as the operative risk is slight, do justify surgical intervention in cases such as that reported here.—Author's Abst.

**The effect of parathyroid hormone and calcium lactate on calcification in pulmonary tuberculosis.** Gordon, B. and A. Cantarow. *Am. Rev. Tuberc.* 20: 901. 1929.

Parathyroid extract was administered to 60 tuberculous patients to determine the effect upon symptoms, calcification and the course of the disease. Treatment varied from a few days to five months. Roentgen-ray observations, blood calcium and blood clotting determinations, strength tests, laryngeal examinations, and records of weight, temperature, pulse rate and blood pressure were made. Subjective observations were limited to the occurrence of symptoms. In most instances an increase in blood calcium was maintained. There seemed to be a favorable influence upon strength and on vague muscular pains. Cough and the amount of sputum were diminished in 34 patients; pain of acute pleurisy was relieved in 14 patients and in several instances a decidedly favorable effect upon hemoptysis occurred. There was no apparent change in the activity of the tuberculous processes, except possibly a decrease in exudate. Nineteen patients in the group were observed for three years since cessation of treatment. Calcification occurred in three patients and fibrosis was noted in four instances, but these individuals appeared to have natural tendency to heal. Four patients showed an extension of the disease and the remaining number suggested no definite change. Twenty-nine patients had died and twenty had not been traced. In seven patients examined at necropsy there was no evidence of calcification that would not be expected in the usual process of healing. Since the use of parathyroid extract apparently failed to influence calcification, further studies were made to determine the effects of calcium lactate administered in addition to parathyroid extract. Roentgen-ray studies of the lungs and bones of the hands were made before treatment was instituted for comparison with roentgenograms taken every two weeks during the course of treatment. There was no evidence of calcification or decalcification in the lungs or bones. Symptomatic manifestations, especially 4-8 hours after the administration of parathyroid hormone, were similar to those noted in the first group of patients. The study suggests that the administration of calcium salts and parathyroid hormone may be of considerable value in relieving symptoms and in decreasing certain exudative processes in tuberculous patients. Obviously these influences may have a favorable action on the course of the disease but there are no data to prove definitely that the procedures cause a deposition of lime salts.—Authors' Abst.

**The effects of solar irradiation of long visible and ultraviolet wavelengths respectively, with and without supplementary irradiation of various types, on the growth of chicks and the development of parathyroid glands.** Sheard, C., G. M. Higgins and W. I. Foster. *Am. J. Physiol.* 93: 686. 1930.

Confinement of chicks behind red-purple corax (Corning Glass G 986 A transmitting 270 to 400 millimicrons) or amber glass (Pittsburgh Amber 48, transmitting 500 millimicrons to end of visible spectrum) does not permit normality in development and growth of chicks or of glands. Normal parathyroid glands develop only in the presence of both the visible and ultraviolet portions of radiant energy. Supplementary irradiation of chicks, housed behind the amber filter, with an air-cooled quartz mercury lamp (ultraviolet irradiation of approximately 575 ergs each second for each square millimeter) for ten to fifteen minutes a day induces normal growth and development of parathyroid glands. Ultraviolet irradiation of the heads only of chicks is appar-

ently as effective as (and possibly more so than) irradiation of the bodies and legs only. The ultraviolet portion of sunlight, as transmitted by corex, is not sufficient to compensate for the absence of vitamin D in the diet or the ultraviolet content of unfiltered sunlight. Microscopic investigations (Becke method) on the calcification of tissues (femurs) in chicks about three and five months old, respectively, kept behind either amber or corex filters and given various supplementary amounts of irradiation with the quartz mercury arc, show that normal calcification does not occur in chicks receiving only the long wavelengths of sunlight. Further evidence is presented to support the statement that normal growth of chicks and development of parathyroid glands are dependent on both the ultraviolet and visible portions of solar irradiation, all other factors remaining constant so far as is known.—Authors' Abst.

**Parathyroid tumor and changes of the bones.** Snapper, I. Arch. Int. Med. 46: 506. 1930.

The following points were noted in a patient suffering from extensive decalcification of the bones, combined with violent pain: The illness began as osteitis fibrosa generalisata. Therefore there existed a pseudo-osteomalacic end-stage of Recklinghausen's disease. There was a great increase in the calcium content of the serum. The deviation was considered to be a symptom of hyperfunction of the parathyroids. There was a small swelling in the thyroid. On account of these facts, a tumor of a parathyroid gland was suspected, and was found during operation. After extirpation of this small tumor, clinical recovery occurred.—Author's Summary.

**Vasomotor reflexes following parathyroidectomy.** Stoland, O. O. and A. M. Lands. Am. J. Physiol. 93: 691. 1930.

The vasomotor reflexes were studied in dogs and cats under ether or amylal anesthesia before and two to ten hours after the removal of thyroids and parathyroids. After thyroparathyroidectomy there was found an increase in the irritability of the vasomotor centers as shown by an augmented pressor or depressor response. There was a gradual increase in irritability up to a maximum after which the response was diminished approaching the normal. Clamping the veins from the parts stimulated did not alter the response but denervation completely eliminated response. The results indicate that the increased vasomotor responses occurring a few hours following thyroparathyroidectomy is due to increased irritability of the nervous mechanisms involved. No evidence was found in favor of a pressor autocoid substance liberated from the tissues stimulated as suggested by Vincent and Thompson.—Authors' Abst.

**The excretion of calcium through the intestine.** Taylor, N. B. and A. Fine. Am. J. Physiol. 93: 544. 1930.

There is a small but constant excretion of calcium through the small and the large bowels of normal cats. Calcium injected into the veins of animals kept upon the usual diet of meat scraps and biscuit practically disappears from the blood within 3 hours. The disappearance cannot be accounted for by excretion through the bowels or kidneys. So far as has been determined, the excess calcium does not leave the body. The excretion of the injected calcium through the large and the small bowels is several times greater in parathyroidectomized than in normal animals. The administration of parathyroid extract was found to be without significant effect upon the excretion of calcium through the bowel during a 6-hour period. This was slightly less than that found in normal animals, but the difference was slight and cannot be considered significant.

—Authors' Summary.

**Some effects of the administration of excessive doses of irradiated ergosterol to normal and to parathyroidectomized dogs.** Taylor, N. B., H. D. Branion and H. D. Kay. J. Physiol. 69: 35. 1930.

The normal action of irradiated ergosterol depends on the integrity of the parathyroid glands.—C. I. R.

**The chronaxie of the vagus nerve in dogs given methyl guanidine sulphate and in thyroparathyroidectomized dogs.** Woodbury, R. A. *Am. J. Physiol.* 93: 699. 1930.

The rheobase and chronaxie of the vagus nerve to the heart were determined using 82 stimuli per second during a stimulation period of two seconds. In dogs treated with small doses (10-50 mgm. per kilo) of methyl guanidine sulphate there followed an increased vagus irritability within ten minutes following intravenous injections and in 30 to 60 minutes following subcutaneous injections. Eighty minutes to three hours after the subcutaneous injections the rheobase and chronaxie readings indicate irritability below normal. Larger doses produce decreased irritability followed by increase to above normal. In thyroparathyroidectomized dogs vagus irritability was increased two to four hours after the removal of the parathyroids and continued high during tremors and mild tetany. Following severe tetany or convulsions the increased rheobase and chronaxie readings indicate a fairly marked fall in irritability.

—Author's Abst.

**The physiological action of an acid extract of normal thyroid glands with low iodine content.** Baker, H. L., C. M. Bacon, C. J. Lundy and D. Klein. *Am. J. Physiol.* 93: 630. 1930.

An extract has been prepared from normal thyroid glands, with a low iodine content having the following properties; increases the blood pressure; slows the heart rate; increases blood sugar; lowers the CO<sub>2</sub> capacity of the blood; has no effect on the blood calcium. The rise in blood pressure was secured after vagus section, after atropine, and after the spinal cord had been transected just below the medulla. The slowing of the heart rate was abolished by sectioning the vagi and the use of atropine. Kidney, suprarenal, liver, ovary, pancreas, duodenum, thymus, prostate, spleen and muscle subjected to the same method of preparation did not yield extracts having the properties of the thyroid extract. A depressor substance was found in the same fraction of every tissue studied including the thyroid and excepting the suprarenal gland. The pressor and other properties of the thyroid fraction herein described are not due to thyroxin or di-iodo-tyrosin. Dogs were used as experimental animals.—Authors' Summary.

**Tests of metabolism in patients with exophthalmic goiter: Self-regulation of diseased organism (Stoffwechsel-Untersuchungen bei morbus Basedowii; ein Beitrag zur Kenntnis der Selbstregubierung des erkrankten Körpers).** Boenheim, F. *Klin. Wchnschr.* 9: 497. 1930. Abst., *J. A. M. A.* 94: 1879.

Boenheim determined the basal metabolic rate in 46 patients with exophthalmic goiter. He found that in 37 persons the basal metabolism was increased, in 6 it was normal and in 3 it was reduced. In order to show that in the latter 3 cases the diagnosis of exophthalmic goiter was correct, the author describes 2 of them. In these patients the condition of the basal metabolism and of the specific dynamic action indicates a sort of self-regulation on the part of the diseased organism. As yet it has not been determined what causes this self-regulation nor why it does not become effective in all instances. The author determined the basal metabolic rate and the specific dynamic action also in 10 patients with myxedema. In one patient the metabolic rate was normal, in all the others it was reduced. It was also noted that the specific dynamic action usually is inversely proportional to the basal metabolic rate; that is, the lower the basal metabolism, the higher the specific dynamic action.

**Bacteriology of the thyroid in goitre. II. Some experimental results.** Cantero, A. *Canad. M. A. J.* 22: 343. 1930.

In a study of 110 cases of adenomatous goiter, with or without hyperthyroidism, a non-haemolyzing streptococcus was isolated in 58 cases, a Gram-positive diplococcus in 21, and an apparent diphtheroid bacillus closely related to the streptococcal group in 10 cases. The results are in agreement with those earlier published. Fresh experiments (123) on animals have been made with 37 different strains. It appears as if the thyroid gland in adenomatous goiter in man harbours partial tension organisms belonging to the streptococcal group which when injected intravenously into animals (rabbits) produce en-

largement and hyperaemia of the thyroid, liquefaction, and absorption of colloid, and in certain cases findings which are not obtained with streptococcal strains from ulcers and cholecystitis. The pathological changes are apparently not the result of active multiplication of the organisms. It appears that the thyroid is a favorable spot for lodgment of these strains resulting in the local production of a relatively large amount of toxic material.—A. T. C.

**Operative mortality in hyperthyroidism.** Clute, H. M. J. A. M. A. 95: 389. 1930. Abst., A. M. A.

During a five-year interval, 2,128 patients were operated on for primary hyperthyroidism with fourteen deaths, a mortality rate of 0.65 per cent. In the same five years 641 patients with toxic adenomatous goiter were operated on with twelve deaths, a mortality rate of 1.87 per cent. The total number of patients during these five years who were operated on for hyperthyroidism is, therefore, 2,769. Of this number twenty-six died, a mortality rate for all patients with hyperthyroidism during the five-year interval of 0.93 per cent. Further reduction of the operative mortality in hyperthyroidism below its present low figure can be accomplished by the recognition of the fact that most unexpected mortality arises in patients (1) of 40 years and over; (2) weighing in the neighborhood of 100 pounds, or having large losses in weight and (3) having had well marked hyperthyroidism for more than a year. Thyroidectomy in these patients should in most instances be divided into stages, even though the patient's course on the table seems to warrant the complete procedure. By this arbitrary decision it is probable that a further reduction in mortality can be accomplished.

**Disturbances in carbohydrate metabolism in exophthalmic goiter.** Kugelmann, E. Klin. Wchnschr. 9: 1533. 1930. Abst., J. A. M. A. 95: 1386.

Kugelmann performed levulose tolerance tests on healthy persons and on patients with exophthalmic goiter. In the morning the blood sugar content was tested while the persons were still fasting. Then 100 gm. of levulose was administered and blood sugar tests were made first after fifteen-minute intervals and then after thirty-minute intervals. In healthy persons the blood sugar increases slightly but within two hours has again reached the normal level. In patients with exophthalmic goiter the increase is considerable and even three hours after the administration of the levulose the blood sugar is still much higher than normal. On the basis of his observations the author concludes that in the liver in thyrotoxicosis the glycogen depots are depleted, and the liver is no longer capable of changing large quantities of levulose into dextrose and of storing the dextrose. This demonstrates that in exophthalmic goiter there exists a functional disturbance of the liver, which becomes manifest in the pathologic behavior of the intermediate carbohydrate metabolism.

**Comparative sensitivity to oxygen-want and to sodium lactate of the hearts of normal and thyroxinized animals.** McEachern, D. and E. C. Andrus. Am. J. Physiol. 93: 673. 1930.

The auricles of two rabbits were suspended side by side in a Dale bath. To one animal thyroxin had been administered in graduated doses over a period of two weeks. The authors have confirmed the observation of J. K. Lewis, that the spontaneous rhythm of the thyroxinized heart persists after isolation at a rate conspicuously more rapid than that of the normal. They have further shown: (1) That the auricles of the thyroxinized animals are far more sensitive to the withdrawal of oxygen than the normal. (2) That their rate and amplitude are depressed by doses of sodium lactate which produce little or no effect upon the normal auricles, and (3) that recovery from the above takes place more rapidly in the normal than in the thyroxinized auricles. The authors regard these results as indirect evidence of an accumulation of lactic acid in the heart of the thyroxinized rabbit.—Authors' Abst.

**Pitfalls in the clinical application and interpretation of the basal metabolic rate.** Rabinowitch, I. M. Canad. M. A. J. 23: 152. 1930.

The various standards are dealt with critically. The seasonal, daily, and hourly fluctuations in individuals may amount to several per cent, and are not

the result of technical error. Muscular tone affects the result and a cold bath should never be allowed on the morning of the test. Muscular tone probably accounts for the tendency towards low metabolism exhibited by arthritics. Fever requires application of a correction, while following fever, especially when prolonged, the complication may arise of a lowered metabolism due to resulting exhaustion and undernutrition. Dietary habits affect the result. Heavy meat-eaters tend to have higher metabolic figures. The nervous factor must be watched. There may be an increased metabolism during the premenstrual period, and there is such an increase in the later months of pregnancy. Lactation, and involution of the uterus following pregnancy, cause a slight increase. The first effect of x-ray treatment is usually an increase of the rate. A particular individual may have a rate within the limits usually considered as normal, and yet, if his true normal figure be close to the lower "normal" limit, his actual figure may correspond with an existing hyperthyroidism.—A. T. C.

The effect of Lugol's solution on the metabolic rate of rabbits fed on abnormal human thyroid preparations. Reznicek, C. G. *Am. J. Physiol.* 93: 683. 1930.

Studies were made of the effects upon the metabolic rates in rabbits by feeding abnormal human thyroid gland preparations with and without Lugol's solution. The following preparations were fed in varying daily doses: (1) Fresh hyperthyroid glands desiccated; obtained from the Wisconsin General Hospital, Madison. (2) Preserved (formalin) toxic adenoma and exophthalmic glands desiccated; obtained from and separated into the above grouping by the clinical staff of the Methodist Hospital, Madison. (3) Commercial desiccated thyroid of Lilly (control). The apparatus used for determining basal metabolism was an open circuit type using room air and determining (by weight) the  $\text{CO}_2$  and  $\text{O}_2$ . The general laboratory average for normal rabbits was 2.61 calories per kilo per hour. Forty rabbits were used in this study. The normal metabolic rate for each was determined and desiccated gland was then fed in varying doses until a high level of metabolism was reached. All three of the above preparations acted alike in raising the metabolic rate 40 to 100 per cent above normal. Lugol's solution fed simultaneously in doses of 0.06 cc. daily did not protect the animal from an increase in metabolism. Lugol's solution fed alone caused no change in metabolism. Lugol's solution in doses of 0.06 cc. given to animals previously fed on any of the three thyroid preparations did not lower the metabolic rate.—Author's Abst.

The size of the heart in experimental hyperthyroidism. Simonds, J. P. and W. W. Brandes. *Arch. Int. Med.* 45: 503. 1930.

Feeding 10 gm. of desiccated thyroid daily to healthy dogs can cause an actual hypertrophy of the heart. This hypertrophy is related to the loss of body weight, and occurs in those animals which have lost from approximately 25 per cent to 35 per cent of their original body weight. When the loss of weight exceeds approximately 35 per cent the heart loses the weight it has gained in hypertrophy and the heart weight-final body weight ratio approaches that seen in simple inanition. This hypertrophy involves all of the chambers of the heart with a slightly greater proportional increase in the left ventricle.

—Authors' Summary.

Prolonged treatment of exophthalmic goiter by iodine alone. Thompson, W. O., Phebe K. Thompson, A. G. Brailey and A. C. Cohen. *Arch. Int. Med.* 45: 481. 1930.

Twenty-four patients with exophthalmic goiter (14 mild and 10 severe or moderately severe cases) were treated with iodine alone, either continuously or intermittently for periods ranging from one and one-half months to three years. The period of treatment was a year or more in 13 instances. With three exceptions (all unsatisfactory responses to iodine) the patients pursued their daily work throughout the period of observation, thus eliminating the effect of rest. In 9 of the 14 mild cases (64 per cent) the results were satisfactory; i.e., the clinical evidence of thyrotoxicosis was either completely or almost entirely kept under control, and the basal metabolism was kept at a normal level. In 4 of these 9 cases (in which iodine was omitted from 10 to

16 months) the disease has apparently disappeared, and in three others in which it was omitted from 4 to 17 weeks, there has been no recurrence of symptoms. In 3 of the 14 mild cases (22 per cent) the results were fairly satisfactory; i.e., there was definite improvement in spite of tardiness or fluctuations in the response. In two mild cases (14 per cent) the results were unsatisfactory; the disease did not become worse, however, on iodine. In the 10 severe or moderately severe cases, the results were satisfactory in one (10 per cent); there was no permanent satisfactory benefit in 4 (40 per cent); and the disease became worse in 5 (50 per cent).—Authors' Summary.



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